

20th
EDITION

Handbook of Nonprescription Drugs

An Interactive
Approach to Self-Care

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Foreword

Since 1967, the American Pharmacists Association's (APhA) *Handbook of Nonprescription Drugs: An Interactive Approach to Self-Care* has been the definitive resource for pharmacists and other health care providers as they guide patients in pursuit of high-quality self-care. This twentieth edition continues the proud tradition of providing generations of pharmacists with the comprehensive content they have come to expect from APhA.

And now more than ever, they need it.

The United States is the world's largest market for nonprescription products. According to the Consumer Healthcare Products Association, annual spending on these products is approaching \$40 billion. This number is likely to rise. Growth in self-care is fueled partly by an increase in direct-to-consumer advertising of prescription and nonprescription medications. Information obtained from television commercials, newspaper and magazine advertisements, the internet, and health-related articles also have empowered consumers to make decisions about their health care.

The 2012 National Health Interview Study reported that Americans are increasingly using natural products—also known as dietary supplements—other than vitamins and minerals for self-treatment: 17.7% of U.S. citizens older than 18 years of age and 4.9% of children between the ages of 4 and 17 years. The use of complementary alternative medicine (CAM) therapies, dietary supplements, nondrug measures, diagnostic tests, and medical devices also is changing self-care. Unlike nonprescription medications, no federal regulatory agency evaluates the safety and effectiveness of CAM therapies.

Individuals who wish to self-treat minor health disorders are faced with a staggering number of single-entity and combination nonprescription products, and they may lack adequate information to determine whether their medical disorder is amenable to self-treatment and whether the self-selected treatment is appropriate for them. An anticipated increase in the number of prescription medications that will be reclassified as nonprescription will provide new self-care possibilities.

Expanded options mean more complexity and more demand for pharmacists'

expertise.

Limited clinical evidence as to self-care products' safety and effectiveness, and the potential for serious adverse events when they are combined with prescription or nonprescription medications, puts health care providers' expertise on alternatives to traditional medications at a premium. We must be ready to provide therapeutic information and guidance to our patients. This responsibility requires pharmacists to be on the cutting edge: The twentieth edition of the *APhA Handbook of Nonprescription Drugs: An Interactive Approach to Self-Care* will help you get and stay there.

The information in this edition also is available online through the subscription-based PharmacyLibrary portal at www.pharmacylibrary.com. Here you will find the complete *Handbook* content along with many other complementary resources. Through PharmacyLibrary, APhA also is publishing additional case studies to reinforce key concepts discussed in these chapters.

I am so honored to be the chief executive officer (CEO) of the organization that created this esteemed resource for all health care educators, students, and providers engaged in self-care. This text is a jewel among APhA's excellent and up-to-date resources, and we are exceedingly proud of it.

Scott Knoer, MS, PharmD, FASHP

Executive Vice President & CEO

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Preface

The newly revised and updated twentieth edition of the *Handbook of Nonprescription Drugs: An Interactive Approach to Self-care* is a comprehensive and authoritative textbook on self-care and nonprescription medications. Written and reviewed by experts in practice and academia, this edition of the *Handbook* continues to serve as an authoritative source for students and health care providers who guide and care for individuals undertaking self-treatment. The major goals for this edition were to

- enhance the content in all chapters from the previous edition with up-to-date information that is beneficial to all health care providers and students.
- update the objectives to complement the content in the chapters that focus on medical disorders.
- create an accompanying “Emerging Issues” chapter (available at pharmacylibrary.com/updates) that will provide information on evolving self-care topics that do not fit into any of the published chapters.

This edition remains true to the spirit of previous editions, that is, to assist health care providers and students in developing the knowledge and problem-solving skills needed to

- assess a patient’s health status, medical problems, and current practice of self-treatment, including nonprescription and prescription medications, dietary supplements, and other self-care measures.
- determine whether self-care and/or self-testing and monitoring are necessary and/or appropriate.
- recommend safe and effective self-care measures, taking into account the patient’s treatment preferences, where appropriate.
- Removal of the pregnancy risk categories for all drugs and natural products, and subsequently, the removal of the two appendices that focused on pregnancy risk information.

The following explains the reasoning for this decision:

In 2015 the Food and Drug Administration (FDA) implemented the

Pregnancy and Lactation Labeling Rule (PLLR), which replaces the former pregnancy risk letter categories (A, B, C, D, X) for prescription drugs with more descriptive content in the following fields^{1,2}:

- Pregnancy: now includes labor and delivery
- Lactation
- Females and males of reproductive potential

Although this new categorization provides clinicians with more detail for decision making, clinicians still need to apply this information on a case-by-case basis. The PLLR will be implemented in phases, with the final phase to be completed by June 29, 2018. However, this rule is not applicable to self-care and nonprescription products.

Previous editions of the *Handbook* have included pregnancy risk letter designations, where available, and oftentimes this was based on the designation for the prescription version of the medication. With the changes that have taken place and the lack of support for letter designations to identify pregnancy risk, the editors decided to remove any reference to a pregnancy risk category within chapters, and to remove both appendices. Where this information appeared previously we now include general language that supports the reader in determining, based on available literature, what is best for their particular patient in each situation. The following is the standard language in all chapters that mention medication or product use in pregnancy:

- See the Preface for a detailed explanation of the pregnancy data.
- Use in pregnancy should be limited to clinical situations in which the potential benefit justifies potential risk to the fetus

Where a pregnancy issue exists for a nonprescription product, the Drug Facts Label states that the consumer should ask a health care professional before using the product if she is pregnant or breastfeeding. FDA is aware of the limitations of the Drug Facts Label for communicating complex issues such as pregnancy labeling. They attempt to ensure nonprescription labeling is as consistent as possible with the prescription drug labels when a drug is available in both forms. However, the challenge with nonprescription products is to provide information that consumers can understand but is detailed enough to address any concerns. FDA is aware of the inconsistencies this situation has created and, at the time of this writing, was discussing options to

enhance the pregnancy content for nonprescription products.

As with the previous edition, an online version of the book resides on APhA's digital platform PharmacyLibrary (www.pharmacylibrary.com), which allows regular updating and/or revision of chapters. With this edition, purchasers of the print book will have access to the online updates and revisions at <https://pharmacylibrary.com/updates>. For the print and online versions of the book, two new comprehensive patient cases per chapter are included; these cases are based on the revised nineteenth edition case format. The online version of the book provides additional cases that are based on the abbreviated case format used in previous editions.

Self-care opportunities exist for many individuals with myriad health disorders. The discussion of these disorders in this book lends itself to the following objectives. For each patient complaint

- identify its most likely underlying cause(s).
- identify common signs and symptoms.
- determine whether the complaint is amenable to self-care, the patient requires referral, or nothing needs to be done.
- identify the FDA-approved monograph active ingredient(s) in a given nonprescription drug category or drug that would best treat the complaint.
- determine common side effects for a drug or a given category of nonprescription drugs.
- determine contraindications to the use of a given drug or category of nonprescription drugs or devices.
- distinguish indications and limitations for use of a given drug or category of nonprescription drugs or devices.
- explain nondrug measures commonly used in treatment or prevention.
- develop an appropriate care plan for a given patient who seeks self-care advice.
- formulate a list of key counseling points to educate a patient on the appropriate use of a nonprescription drug, nondrug measures, or a device.

Considerable time and effort have been invested in improving this edition. We are hopeful that each of the chapter enhancements and updates improves the quality and usability of the book, as well as provides increased clarity and convenience.

Chapter Content

All disorder-related chapters in this edition include the following features and information:

- Up-to-date information on nonprescription medications, including indications, dosages, interactions, supportive evidence for efficacy and safety, medical disorders or symptoms amenable to self-treatment, prescription-to-nonprescription reclassifications, and nonprescription drug withdrawals from the market
- Treatment algorithms that outline triage and treatment
- Controversies in self-care therapeutics
- Self-care treatment or prevention guidelines
- Product tables with examples of specific nonprescription products
- New nonprescription medications and dietary supplements, including nutrition-related dietary supplements, such as vitamins and minerals, which are discussed in the nutrition section of the book

Chapter Features

Most chapter features remain unchanged and are intended to promote an interactive approach to self-care. Students and health care providers can use these features to develop or improve problem-solving and critical thinking skills.

- Disorder-related chapters are grouped primarily according to body systems. These chapters begin with a discussion of the epidemiologic, etiologic, and pathophysiologic characteristics and the clinical manifestations of the disorder. These discussions are followed by a comprehensive discussion of self-care options. The inclusion of dietary supplements, as well as nonpharmacologic and preventive measures, completes the discussion of self-care options. Information about one preventive measure, vaccines, is incorporated in chapters in which the content is deemed synergistic.
- Case studies, treatment algorithms, comparisons of self-treatments, patient education boxes, and product selection guidelines foster an interactive therapeutic approach to learning.

- The case studies in the Handbook utilize the Pharmacists' Patient Care Process (PPCP) format which is described in detail in [Chapter 2](#). The online case studies utilize the QuEST/SCHOLAR-MAC process. These are consistent with previous editions.
 - Sections on the evaluation of patient outcomes reinforce follow-up of patients who are self-treating. This section defines the parameters for confirming successful self-treatment and those that indicate the need for medical referral.
 - Chapters include tables that list interactions (drug–drug, drug–supplement, drug–nutrient), as well as dosage and administration guidelines.
 - At the end of each chapter, authors provide a list of key points. These are intended to serve as a summary of critical information in the chapter and can be an excellent resource for educators.
 - Authors provide comparisons of agents based on clinical studies of safety and efficacy, as well as product selection guidelines based on patient factors and preferences.
 - Authors discuss the role of nonprescription therapies among the available treatment options for a specific disorder and describe other options in the event that nonprescription therapy fails or is not appropriate.
 - The book's organization and content allow students and health care providers to quickly identify the information needed to make a treatment recommendation and to counsel patients.
-

Acknowledgments

We would like to acknowledge the hundreds of individuals who contributed to the new edition of this textbook. We are grateful to each of the authors and reviewers who contributed to this comprehensive and authoritative textbook. These individuals were selected from many practice settings and health professions throughout the country. Their scholarship and clinical experience reflect a broad perspective and interdisciplinary approach to patient care. The dedication of the authors and reviewers in ensuring that the chapters were accurate, comprehensive, balanced, and relevant to practice and of the highest quality is deeply appreciated.

The editors of this edition also want to acknowledge the contributions of

previous editors, authors, reviewers, and the many health care providers, students, residents, and others who have helped make the *Handbook of Nonprescription Drugs* the premier resource for self-care content. We also want to thank the staff of the American Pharmacists Association, in particular John Fedor, Jesse Vineyard, and Janan Sarwar, for their ongoing support of our vision for the content and its incorporation into the print version and the online version available at PharmacyLibrary.com.

We would like to convey a very special thanks to Linda Young, our managing editor. Once again Ms. Young provided invaluable guidance and support to the editors, authors, and reviewers in all aspects related to the publication of this edition. She contributed to the copyediting of chapters, and managed the design, editorial, and composition stages of the book. Without her tireless efforts, experience, and attention to detail, the improvements in this edition would not have been possible.

We are confident that the combined efforts of these individuals will ensure that the *Handbook of Nonprescription Drugs: An Interactive Approach to Self-Care* continues to serve as the worldwide practice and teaching resource on self-care and nonprescription products.

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Chapter 1: Self-Care and Nonprescription Pharmacotherapy

Authors: Jenelle L. Sobotka, Barbara A. Kochanowski

This chapter introduces the concept of self-care, delineates characteristics of today's self-care consumer, and examines the growing importance of self-care in modern health care systems. *Self-care*, as defined by the Global Self-Care Federation, is “[t]he practice of individuals looking after their own health using the knowledge and information available to them. It is a decisionmaking process that empowers individuals to look after their own health efficiently and conveniently, in collaboration with health and social care professionals as needed.”¹ As discussed in this chapter, the pharmacist has a key role in providing assistance, advice, and information to address self-care needs. An overview of the self-care marketplace, as well as the legislative and regulatory environment, is presented first, with a brief perspective on future changes expected for expansion of self-care and related health care technology.

Broad public education has been shown to be a key factor in advancing the consumer's role in prevention of illness and general health management; accordingly, several public education programs are reviewed in this chapter to illustrate pharmacists' role in supporting this effort. The chapter concludes by reviewing the roles of the pharmacist and student pharmacist in assisting patients with their self-care needs, while emphasizing the key elements of safety and efficacy in the management of self-care conditions.

The Expanding Definition of Self-Care

A simple definition of *self-care* is as the independent act of preventing, diagnosing, and treating one's illnesses with or without seeking professional advice. However, self-care definitions can vary according to one's perspective, with health care professionals' definition frequently differing from that of the general public. Health care providers (e.g., doctors, pharmacists, nurses) typically consider self-care to include the clinical management of self-care conditions and use of relevant self-care products available to patients without a prescription. Health care providers who wish to acknowledge the expanded role for today's pharmacists would add that self-care should include assistance

in determining whether a patient's condition is appropriate for self-care. Pharmacists are accessible to patients when most self-care decisions are made and are valuable experts in this area. A pharmacist can help the patient improve by recommending the best nonprescription product for treatment of the condition and/or identifying beneficial nonpharmacologic measures (e.g., dietary or lifestyle changes). Such measures also may be helpful to prevent further occurrences of the condition. In this context, the process becomes "pharmacist-assisted self-care." The primary focus of this book is the pharmacist's role in this process but also introduces roles that student pharmacists can assume as they develop their patient care skills for self-treatable conditions. Other health care providers (e.g., nurse practitioners, physician assistants) who also may be involved in advising patients on self-care will find significant applications of the concepts, content, and processes provided in this book.

Consumers' perspective and their definitions of self-care can differ considerably from those of health care providers. When consumers were asked to describe what self-care involves, their responses went far beyond the use of nonprescription medications.² The consumers listed healthy habits, such as diet and exercise, but they also noted other important aspects of self-care: screenings and wellness check-ups, preventive care, consultations with doctors, and their own participation in deciding how to deal with a health problem. All of these factors represent consumers' increasing interest in and expectation to be accountable for their own health and wellness. In the United States, "personal accountability" to manage and improve health is expanding the general public's definition of self-care.

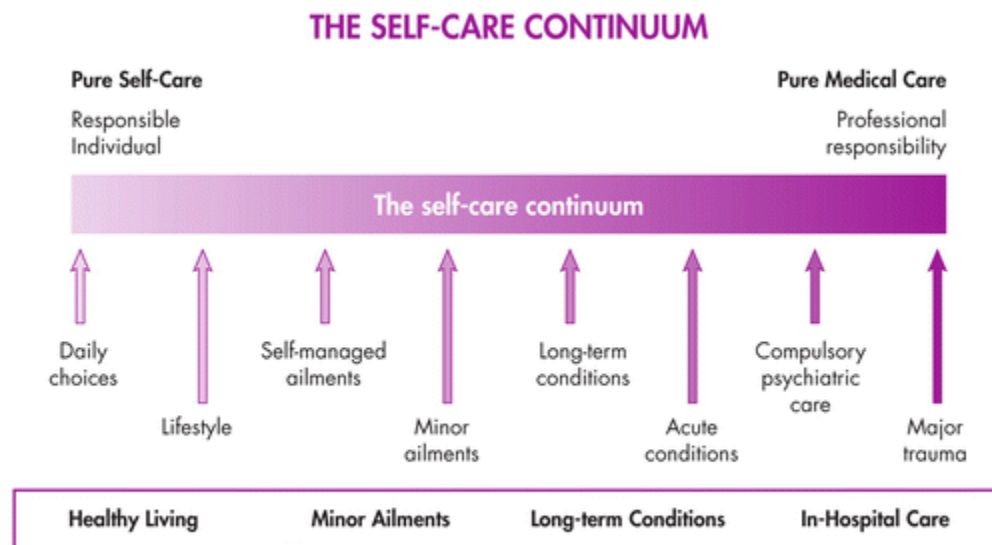
The engagement of a health care provider easily differentiates pharmacist-assisted self-care from self-care. However, when does pharmacist-assisted self-care undergo transition to primary care in a more contemporary health care system? Many people who are not health care professionals turn to Wikipedia to find common definitions. Wikipedia defines *primary care* as "the day-to-day health care given by a health care provider. Typically, this provider acts as the first contact and principal point of continuing care for patients within a health care system, and coordinates other specialist care that the patient may need."³ Is the pharmacist considered a health care provider under this definition? Is the pharmacist serving as the first point of contact and a principal point of ongoing care for the patient? Many would answer "yes" to these questions, in recognition of pharmacists' evolving role in providing patient care services and

medication therapy management (MTM) in their practice settings. In addition, state and federal legislation to secure pharmacists' recognition as "health care providers" is further advancing this belief.⁴ Continued delivery of patient care services, such as immunizations and point-of-care testing, also will advance the public's recognition of pharmacists as primary care providers. In the future, these efforts will contribute to further blurring of the distinguishable differences between pharmacist-assisted self-care and primary care delivery by pharmacists.

The patient-centered care model of health care delivery is gaining popularity as part of ongoing health care reform in the United States. The Institute of Medicine defines *patient-centered care* as "providing care that is respectful of and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions."⁵ This definition implies that patients and their team of health care providers must have a strong partnership and make decisions together based on the patient's desires and priorities for his or her health goals. As John Gans, former chief executive officer of the American Pharmacists Association (APhA), often said, "All care is self-care!" His point was that the patient is always in charge and will make the final decision on implementing any actions to try to improve his or her health. A key area of emphasis in the patient-provider partnership is the recognition and integration of cultural beliefs, values, and traditions, because these also play an important role in a patient's personal health care decisions. (See [Chapter 3](#) for further discussion of cultural competency in health care.) Furthering advancements in patient-centered, team-based care will involve an interprofessional team of providers who honor the health care priorities of the patient.

It also is important to note that self-care involves the full spectrum of care, including prevention and wellness strategies, diagnosis and screening, and measures for treatment of or relief from symptoms. Preventive self-care involves maintaining well-being and appearance, both subjective and objective, through a healthy lifestyle. For many people, a healthy lifestyle includes controlling the diet; taking vitamins, minerals, and herbal supplements; participating in regular exercise and keeping fit; and maintaining physical appearance with use of dental, skin, and hair care products. By contrast, self-care for persons who are ill involves identifying (diagnosing) the responsible condition and then obtaining products for mitigating illness and relieving symptoms. Examples of selfcare measures in

illness are dietary options (e.g., consuming hot soup for a cold); utilization of certain medical devices for both disease assessment (e.g., home blood glucose meters, cholesterol tests) and treatment (e.g., ice packs, first aid bandages, vaporizers, nasal strips); and use of nonprescription medications (e.g., pain relievers, cold medicines). The use of self-care products typically is limited to cases involving mild illness or short-term management of more acute conditions, and most products warn users to contact a health care provider if improvement is not obtained within a short period of time. In some instances, however, self-care involves long-term management of ongoing symptoms or chronic conditions with nonprescription medications, even when such regimens are recommended by a physician. For example, acetaminophen may be used for the ongoing management of arthritis pain. [Figure 1-1](#) provides a depiction of the self-care continuum, extending from “pure self-care with individual responsibility” to “pure medical care with professional responsibility,” as described by the Self Care Forum.⁶



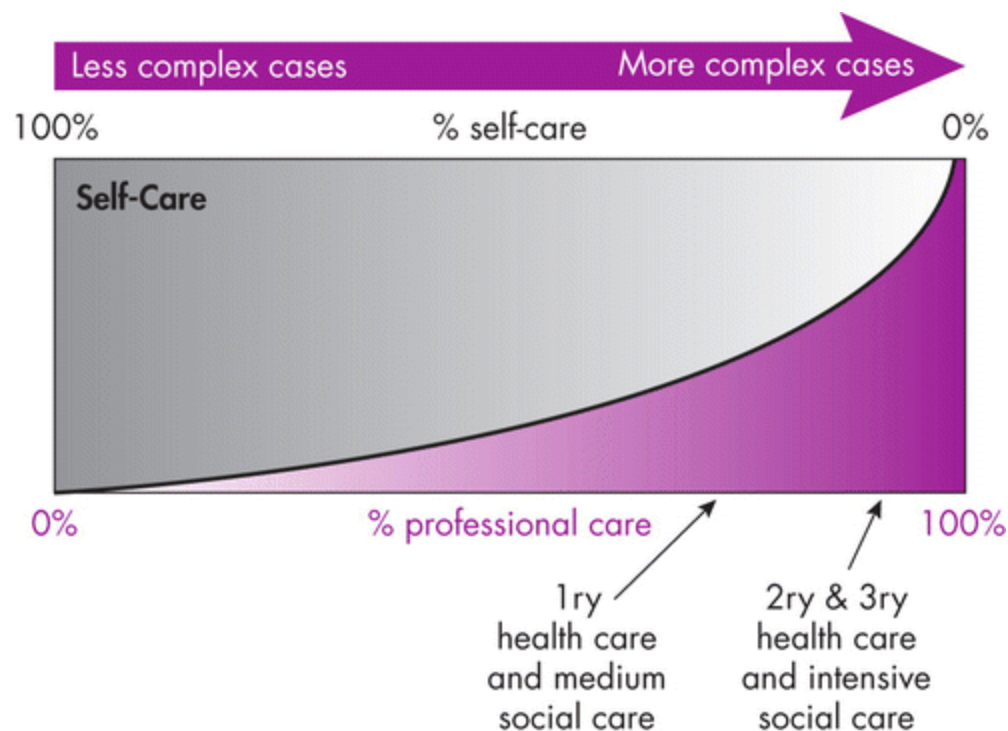
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Figure 1-1 Self-care continuum developed by the Self Care Forum. (Source: Adapted from [reference 6](#) with the permission of the Self Care Forum. Copyright © 2015.)

Globally, both the importance of self-care in the overall health care spectrum

and the role of the pharmacist are gaining additional visibility. In 2017, the International Pharmaceutical Federation (FIP) released both a reference paper and a policy statement on self-care.^{7,8} The reference paper provides a global view of the growing role of pharmacists in self-care and improvement of population health around the world. The policy statement provides recommendations to government agencies and insurers, pharmacy organizations, and pharmacists to advance the adoption of selfcare in health systems around the world. These documents serve as position statements and educational tools for promoting the growing role of pharmacists in self-care to improve global health.

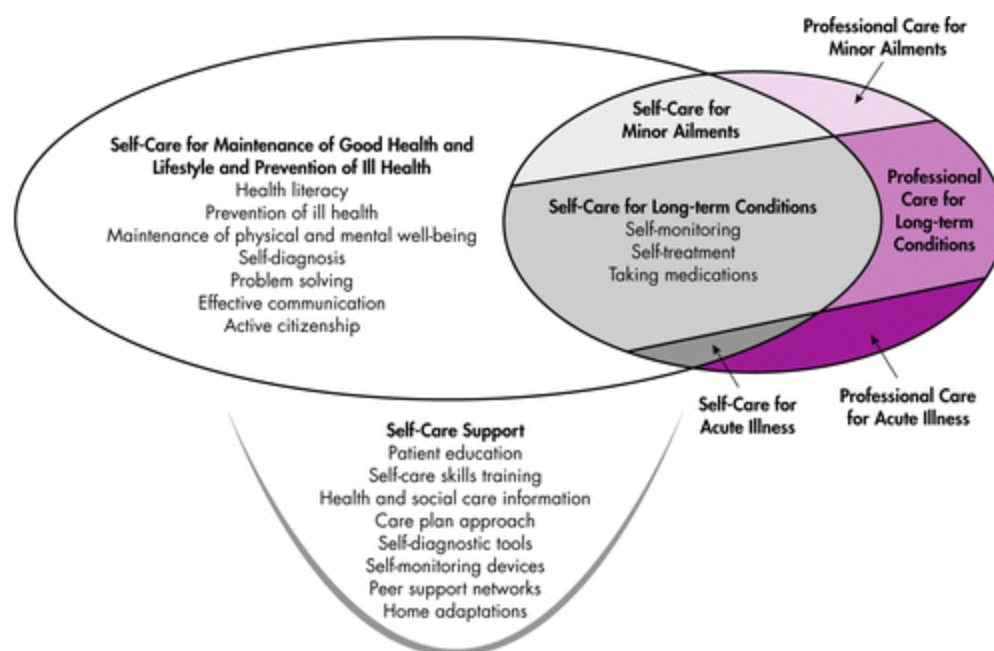
The FIP reference paper refers to an earlier 2005 report from the London Department of Health that highlighted the large role that self-care plays in the total health care model (Figure 1-2).⁹ For professional care, Figure 1-2 includes primary health care as basic medical care, along with secondary and tertiary health care as more complex medical care services (e.g., specialist physicians, intensive hospitalization care). Self-care, when compared with professional care, is shown to be a much larger component in the individual patient's overall health care experience. The FIP paper also references the same London Department of Health report for promoting the importance and supporting the value of self-care behaviors for improved population health, as shown in Figure 1-3.⁹ Professional care for treatment of minor ailments, acute illness, and long-term conditions is depicted in the crescent-shaped area of the oval section on the right of the model. The patient's self-management of these same minor, acute and long-term health conditions is depicted as a larger component of the oval. To the left in the model, preventive self-care measures, important for good health and illness prevention, are depicted as a large component of self-care that does not involve professional care. Again, this model conveys visually the important concept of the very significant role of self-care within the overall health care spectrum. The lower section of the model identifies many important elements for supporting patients' self-care measures. Pharmacists would use most of these elements as tools and processes to assist their patients in implementing self-care approaches.



Most care is shared care and can involve a small or large component of self-care.

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Figure 1-2 Role of self-care in the total health care model. Key: 1ry = Primary; 2ry = secondary; 3ry = tertiary. (Source: Adapted from [reference 9](#) with the permission of the Department of Health, UK.GOV; contains public sector information licensed under the Open Government License v1.0.)



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Figure 1–3 Self-care and self-care support. (Source: Adapted from [reference 9](#) with the permission of the Department of Health, UK.GOV; contains public sector information licensed under the Open Government Licence v1.0.)

The International Self-Care Foundation offers additional evidence of the broad scope of self-care, as illustrated by their seven pillars of self-care, shown in photograph 1 of the [Color Plates](#) and outlined in [Table 1–1](#).¹⁰ Clearly, self-care is significant to global health care to manage or treat active conditions and to address preventive health and wellness.

Table 1–1 Seven Pillars of Self-Care as Defined by the International Self-Care Foundation

Self-Care Component	Description
Health literacy	Includes the capacity of people to obtain, process, and understand basic health information and services needed to make appropriate health decisions
Self-awareness of physical and mental condition	Includes knowing one’s BMI, cholesterol level, and blood pressure; engaging in health screening
Physical activity	Practicing moderate intensity physical activity, such as walking

Self-Care Component	Description
	or cycling, or participating in sports at a desirable frequency
Healthy eating	Includes eating a nutritious, balanced diet with appropriate level of caloric intake
Risk avoidance or mitigation	Includes quitting tobacco use, limiting alcohol use, being vaccinated, practicing safer sex, and using sunscreen
Good hygiene	Includes washing hands regularly, brushing teeth, and washing food before consumption
Rational and responsible use of products, services, diagnostics, and medications	Includes being aware of dangers, using responsibly when necessary

key: BMI = Body mass index.

Source: Adapted from reference

Understanding Today's Self-Care Consumer

Consumers today are motivated and empowered by their ability to use self-care to manage their health. They feel less dependent on physicians and want more control over their health care. Consumers appreciate the availability and convenience of nonprescription medications that enable them to self-treat minor illnesses or injuries, thus avoiding unnecessary inconvenience and copays for treatment from a medical provider.

A survey by the Consumer Healthcare Products Association (CHPA) asked consumers for their perspectives on the role of nonprescription medications in their self-care.¹¹ A key finding was that consumers trust nonprescription medications, when they are available, for health care management for themselves and their children. Key drivers of trust were effectiveness, adverse effects, and doctor recommendation. Consumers also prefer using a nonprescription over a prescription medication for first-line therapy and for certain ailments such as pain, cough and colds, acid reflux, and upset stomach. Additional data collected in the survey “Your Health at Hand: Perceptions of Over-the-Counter Medicine in the U.S.” support the view that both consumers

and physicians recognize the role of nonprescription medications in self-care. Key survey results include the following¹²:

- 93% of physicians believe that medications for minor ailments should be available over the counter.
- 96% of consumers believe that nonprescription medications make it easy to care for minor medical ailments.
- 87% of physicians and 89% of consumers believe that use of nonprescription medications is an important part of overall and family health care.
- 93% of adults prefer to treat minor ailments with nonprescription medications before seeking professional care.
- 88% of physicians recommend that patients address minor ailments with self-care, including the use of nonprescription medications, before seeking professional care.

Today's consumers also are much more knowledgeable about health care products and health care in general. In addition, consumers are more motivated to focus on their health and wellness. For example, consumers are making lifestyle changes, such as drinking more water, taking supplements and vitamins, and eating and exercising more responsibly. Employers, through employee wellness programs, also are offering incentives to improve health. Nearly 90% of employers now offer wellness incentives, such as financial rewards or prizes, to employees who work toward becoming healthier.¹³

The CHPA survey also showed that one in four respondents self-identified as a “family health influencer” based on being knowledgeable about nonprescription medications and playing a role in educating others in the family about their self-care options.¹⁰ These influencers report that they are knowledgeable about different nonprescription medications, they avoid going to the doctor unless they absolutely have to, and they choose a medication on the basis of the symptoms it will treat. The family health influencer is more likely to be female, and many are mothers in the family unit. In addition, the survey found that multigenerational households, Hispanic households, and households that provide care for an adult outside the home place a high value on a pharmacist's or other in-store health care provider's recommendations. Health care providers must acknowledge and partner with this family health influencer in their caregiver role for the family. Other influencers also may be involved in decision making, as depicted in [Figure 1-4](#).¹¹

Figure 1–4 Influencers of consumers’ self-treatment decisions. (Source: Reference 11.)

Internet sources of health information have become increasingly popular across all age groups and demographic populations. Web-based health information is easily and rapidly accessed in the privacy and comfort of one’s home. According to a 2013 Pew Internet and American Life Project report, 59% of U.S. adults searched for online health information in the previous year.¹⁴ Most health information seekers, 77%, begin with a major search engine, such as Google, Yahoo, or Bing, whereas another 13% use a more health-specific site such as WebMD. The report has identified approximately one third of adults (35%) as “online diagnosers” because they have gone online to diagnose their own or someone else’s medical condition.

Consumers who were most likely to search for health information online were white adult women with higher levels of education and income. Dependence on the internet for self-care information can be problematic. No single organization is accountable for the quality or accuracy of health-related information available on websites. The sheer number and diversity of internet sources increase the likelihood that patients may unknowingly view biased or outdated information. When asked if the information found online led them to think they needed the attention of a medical professional, 46% of online diagnosers answered “yes,” demonstrating the potential role for a pharmacist to provide accurate information and answer questions. All health care providers, including pharmacists, should assist their patients in identifying credible resources for health information. A number of valid internet sources are available to provide information on nonprescription drugs; these include the National Institutes of Health (www.nlm.nih.gov/medlineplus) and websites such as those for the Cleveland Clinic (www.clevelandclinicmeded.com), WebMD (www.webmd.com), the Mayo Clinic (www.mayoclinic.com), and the CHPA Educational Foundation (www.knowyourOTCs.org).

In addition to increased access to health care information, consumers need to be able to understand basic health information to make appropriate health decisions. *Health literacy* is the umbrella term that refers to “the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health

decisions.”¹⁵ Health literacy includes numeracy skills, for example, understanding laboratory values, selecting the proper dose of a medication, and reviewing medical bills. The National Assessment of Adult Literacy showed that only 12% of adults have proficient health literacy and 30% of adults have below-basic levels of health literacy.¹⁵ Health literacy affects people’s ability to navigate the health care system in a variety of areas: filling out forms, locating physicians and services, discussing their health information, and selecting a community pharmacy and pharmacist to support their engagement in self-care. Low-level literacy has been linked to poor health outcomes, such as higher rates of hospitalization and less frequent use of preventive services.¹⁵

Health care providers need to be aware that health literacy varies across the population they serve and that they may need to tailor their own language to try to match the patient’s skill level. One approach is to use “plain language”—that is, communication that patients can understand the first time they read or hear it. Key components of plain language include putting the most important points first, breaking complex concepts into chunks (small bits of information), adhering to simple wording, defining technical or medical terms, and using the active voice in which the subject performs the action. Resources for more information include Plain Language.gov (www.plainlanguage.gov) and the Centers for Disease Control and Prevention (CDC) health literacy training module (www.cdc.gov/healthliteracy/training).

The changing demographics of this country’s population also are changing the profile of the self-care consumer. The growth of the older population, whose members are heavy users of nonprescription medications, will continue to expand the self-care consumer base. The results of the 2017 National Projections by the U.S. Census Bureau found that by 2030, all baby boomers will be older than 65 years of age.¹⁶ The average life expectancy for Americans has increased, with people who attain 65 years expected to live an additional 16–22 years, depending on gender and race. The fastest growing segment of the elderly population is that consisting of persons older than 85 years. The racial and ethnic diversity of the older population also will change as the populations of Hispanic and non-White groups increase. These specific groups will have a significant impact on the future of U.S. health care policy and the health care system as their individual members deal with illness and disability and need longterm care and other resources.

The growth in minority populations in the United States will drive a need for

cultural considerations in self-care recommendations. [Chapter 3](#) provides details on cultural considerations in self-care. [Chapter 2](#) provides additional details on self-care for special populations, including geriatric patients, infants and children, and pregnant and breastfeeding patients.

In summary, today's consumer is more empowered and more likely than ever before to take charge of his or her health, often turning to nonprescription medications as first-line therapy options for a variety of conditions. In the decades ahead, the older population will continue to expand and will need information and health care resources, including pharmacists, to manage their health.

Self-Care Changes Driven by Health Care Reform and Changes in Pharmacy Practice

In addition to the consumer factors that affect self-care utilization, notable drivers for self-care utilization are arising from the reform occurring in the U.S. health care system. The passage of the Affordable Care Act (ACA) in 2010 was a key factor in stimulating health care reform. The legislation called for changes to many areas of the U.S. health care system, with a focus on increasing access and quality while decreasing costs. However, even beyond the ACA requirements, the health care market and delivery systems have been actively adopting additional changes that focus on achieving the same goals.

Reform efforts are affecting many areas of the health care system: changes in financial models to drive cost savings, tools and processes to assess and improve care quality and patient satisfaction, and new approaches to maximize health care delivery models. Creative financial models are being tested: They feature approaches such as bundled payments and value-based purchasing, as well as new organizational structures, including accountable care organizations, that bring both financial risk and shared savings opportunities to multiple stakeholders in the health care delivery model. In these new models, providers are even more involved and accountable for the financial impact of health care choices and their patients' clinical outcomes. Patients also are bearing more of the financial burden and accountability for their health care costs through increasing use of high-deductible health care plans and health savings accounts. Quality assessment processes and a focus

on indicators of positive outcomes are expanding in all areas of health care. These processes incentivize health care providers to work in closer partnerships with patients to provide health improvement recommendations that patients will adopt to achieve better health outcomes.

Reform also is changing health care delivery to more of an interprofessional team-based model, in which health professionals from multiple disciplines practice together with a patient-centered focus. This approach should improve the coordination of care for an individual patient across the health care system, while also resulting in improved communications, outcomes, and cost efficiencies in care delivery. Reform, often through legislative changes, also is driving all health care providers, including pharmacists, to expand their scope of practice and to perform at the top of their capabilities in delivering the most cost-effective care. An overall shortage of primary care providers in the United States has led to an expanding role for nurse practitioners and physician assistants in primary care, while also further increasing demand for the pharmacist's expanding role in self-care support and patient care services. Implementation of these reform efforts across the health care continuum is leading toward the common goals of improving health care quality, access, and delivery, while also helping to better manage costs.

Of considerable importance, many of these health care reform activities also can be linked to influencing changes in the selfcare arena. Because health care reform is attempting to improve access, it is driving both patient-initiated self-care and pharmacist-assisted self-care as obvious areas for expansion. The growth of urgent care clinics, some located within pharmacies, is driven by a need for better access to primary care. It will be interesting to monitor potential future practice partnerships between pharmacists and other health care providers in these settings and to assess how these partnerships affect delivery of primary care and pharmacist-assisted self-care support.

Insurance plans also are attempting to enhance the use of self-care initiatives by patients covered under their plan, including the involvement of pharmacists. Some payors have contracted with companies such as OutcomesMTM that compensate pharmacists for providing MTM services, including comprehensive medication reviews that include a detailed review of nonprescription medications, vitamins, and supplements. Pharmacists provide MTM services, document the medication-related problems and action steps taken to improve patient outcomes, and then submit a claim and receive

payment. Data from OutcomesMTM indicate a positive return on investment (ROI) of 15% in drug product costs (\$1.15 for every \$1.00 spent) and total estimated cost avoidance for other medical expenses (\$5.44 for every \$1.00 spent) through the delivery of MTM services in one health care plan.¹⁷ In other words, the insurance plan pays less in total health care costs because pharmacists' MTM interventions serve to avoid unnecessary physician office visits, emergency department visits, and hospitalizations. It is hoped that the positive ROI, improved access to care, and enhanced access to pharmacist-assisted self-care will encourage insurers to continue to expand their new payment models for pharmacists' MTM services.

The incentive for stretching their health care dollars often drives consumers to rely on self-care. More individual patients and families now have high-deductible insurance plans with potential significant out-of-pocket costs. These patients may see self-care as a less expensive option to other medical interventions. However, consultation with a pharmacist or other health care provider can determine when self-care steps are appropriate or when medical referral is necessary. Many people have an employee health savings account that is funded with pretax dollars. Again, self-care can help minimize the spending from this account, so the monies saved can be used for more serious medical issues. For example, a patient with high initial out-of-pocket costs presents to the pharmacy with a sore throat; the cause of the ailment determines the financial consequences of the visit. Either of two scenarios, based on the QuEST/SCHOLAR-MAC process¹⁸ (see [Chapter 2](#)), is possible: (1) The pharmacist determines that the patient likely has a viral condition and that nonprescription products can be used to help treat the symptoms; or (2) the pharmacist determines that the patient likely has strep throat, a bacterial infection that requires antibiotics, and refers the patient to a prescriber. In scenario 1, avoiding an unnecessary and potentially costly physician visit is very important because of the burden of initial out-of-pocket fees. In such instances, patients will find their pharmacist to be an accessible, valuable resource to help them sort through the specifics of their condition to determine whether a medical appointment is truly necessary or whether self-care is appropriate. In addition to improved access and decreased medical expenses, self-care also offers medications and devices that typically, but not always, are far less expensive than similar prescription products. Occasionally, it may be less expensive for the patient to pay the office visit and prescription copayments because an appropriate nonprescription product or device is more expensive. However, the cost in the insurance plan for this level of health

care would be substantially more and would contribute to overall higher health care delivery costs in the system. The pharmacist can play an important role in evaluating a patient's overall medication costs by comparing the cost of self-care products with that of similar prescription products, taking into consideration the patient's insurance plan copay and deductible.

In 2018, a survey of more than 5000 individuals provided information regarding the value of nonprescription medications and their contribution to cost savings and quality care in the health care system.¹⁹ Data from the survey showed the following:

- Availability of nonprescription products provides \$147 billion in annual savings relative to alternatives, primarily a clinician office visit or phone call. The savings include \$95 billion in avoided medical office visits and diagnostic testing and \$52 billion in medication cost savings through use of nonprescription treatment options rather than prescription medications (Figure 1–5).
- Each dollar spent on nonprescription medications saves approximately \$7.20 for the health care system.
- If medicines currently offered as nonprescription were available only as prescription products, approximately 27 million consumers would no longer seek those products.
- The use of nonprescription medicines provides approximately \$34 billion in potential productivity benefits annually.

Figure 1–5 Total savings with use of nonprescription medications for the U.S. health care system. Key: OTC = Over the counter. (Source: Reference 19.)

The value of self-care is particularly important for the medically underserved and uninsured populations. Without access to self-care, this population often is forced to use a hospital emergency department for immediate health care needs. The importance of self-care to the patient and payer communities—and providers' recognition of this need—will continue to force reforms in health care delivery that address the need for increasing access to health care while decreasing costs.

The role of the pharmacist also is changing in how self-care is delivered to

patients. As pharmacists' roles evolved over the past few decades, considerable change has occurred in the pharmacy profession: Pharmacists are moving from a product-dispensing role to that of patient care provider who helps patients improve their medication use and advances their health and wellness. This evolution is well stated by the Joint Commission of Pharmacy Practitioners (JCPP) vision for the profession: "Patients will achieve optimal health and medication outcomes when pharmacists are included as essential and accountable members of patient-centered healthcare teams."²⁰ JCPP represents the combined interests of national organizations of pharmacy practitioners, who collectively adopted this new vision for the profession in January 2014. To enable this vision, JCPP approved a standardized *Pharmacist's Patient Care Process* (PPCP) in May 2014. The process is discussed in considerable detail in [Chapter 2](#). (See [Color Plates](#), photograph 2.)

At the broader level, the pharmacist's role in MTM is being consistently taught to student pharmacists, as well as practicing pharmacists seeking further education, through the APhA MTM Certificate Training Program.²¹ In this program, the five core elements of the MTM service model are defined. The first core element is the medication therapy review (MTR) to gather and evaluate all of the patient's medications, including nonprescription medications, nutritional supplements, and herbal products. From this review, the pharmacist prepares the second core element, a personal medication record (PMR) to list all the patient's medications and immunization records identified during the review. The pharmacist also prepares the third core element, a medication action plan (MAP) that identifies medication-related and health-related problems, proposed actions, and results of those actions, when known. The process concludes with the last two core elements: intervention and/or referral, followed by documentation of the findings and follow-up plans for the patient's health care needs. It is clear that all five MTM core elements ([Table 1-2](#)) include aspects of self-care, nonprescription products, and lifestyle and behavior modifications to improve patients' health and quality of life.²¹ Most of the following chapters provide comprehensive cases that also demonstrate application of MTM core elements and the PPCP for patients who are candidates for either self-care or medical referral.

Table 1–2 Medication Therapy Management (MTM) Core Elements

Core Element	Components
Medication therapy review (MTR)	Collect and evaluate all of the patient's medications.
Personal medication record (PMR)	List all of the patient's medications and immunizations.
Medication action plan (MAP)	Identify medication-related and health-related problems, proposed actions, and results of those actions, when known.
Intervention and/or referral	Take action with patient or health care providers as needed.
Documentation of the findings and follow-up plans	Record notes of the intervention, recommendations, and ongoing care, as needed.

Source: Adapted from reference 21.

In the past decade, numerous publications have described the value of pharmacists' patient care services in improving health and reducing costs. In 2011, Rear Admiral Scott Giberson was the lead author of the landmark U.S. Public Health Service pharmacy report titled "Improving Patient and Health System Outcomes through Advanced Pharmacy Practice: A Report to the U.S. Surgeon General 2011."²² This 95-page, evidence-based report included results from federal pharmacists' patient care practices, particularly from the Indian Health Service and Veterans Affairs Hospital System, as well as data referenced from other studies that validated the health value provider role for pharmacists within the health care system. Additional research projects and publications also have documented the value of pharmacists' patient care services.^{23–26} Any of these papers can be used to advocate for pharmacists' expanded patient care roles and for their recognition as health care providers. More recent emphasis has been on the pharmacist's role in point-of-care testing, ranging from blood pressure, cholesterol, blood glucose, and bone density screenings to rapid influenza diagnostic tests and pharmacogenomics. In this context, the potential benefit of point-of-care testing for patients who visit the pharmacy seeking nonprescription medications for their influenza symptoms has been well described.²⁷ If the pharmacy had the ability to

conduct rapid influenza diagnostic testing, the pharmacist could determine who were candidates for self-care and who needed to be referred to a primary care provider, resulting in decreased risk of mortality from influenza. The timeliness of this assessment is critical so that antiviral medication can be prescribed and started within the 48-hour treatment window for a referral patient. If the patient did not test positive for influenza, the pharmacist could assist with cough and cold self-care recommendations, as appropriate.

Legislative and regulatory changes also are allowing the expansion of pharmacists' patient care services. In numerous states, current and new legislation is allowing pharmacists to enter collaborative practice agreements (CPAs) with prescribers.²⁸ These agreements allow prescribers (primarily physicians) to delegate numerous activities to the pharmacist, including modifying, initiating, or discontinuing patients' drug therapy and ordering laboratory tests. The National Alliance of State Pharmacists

Associations released a report, "Key Elements for CPA Legislative and Regulatory Authority," that offers guidance for further state legislation needed to support this expanding practice area.²⁹

Recently, a study to look at the role of pharmacists in expanding access to care was initiated in the state of Washington.³⁰ Care provided for 20 minor ailments by community pharmacists will be compared with the care received in physician offices, urgent care clinics, and emergency departments. Working under CPAs, pharmacists participating in this study managed patients with conditions that may require prescription therapy and, when appropriate, referred patients for medical care. In other cases, nonprescription therapy and/or nondrug management were recommended when prescription medication or medical care was not warranted. Data collection is now complete, and analysis and reporting of results from the study are in progress. Comparisons of quality of care, costs per episode, and frequency of follow-up care, along with a review of health outcomes, will be made. Although the study includes the 20 minor ailments listed in [Table 1–3](#), pharmacists in the state of Washington are also comprehensively managing, monitoring, and initiating drug therapy through CPAs for many other conditions. Changes in pharmacy design and operations also are in progress to improve the accessibility and visibility of pharmacists. For example, Walgreens is testing small, pharmacy-only stores to provide more targeted access to medicines and pharmacists.³¹ Similar attention to changes in pharmacy layout and workflow is emerging in

other community pharmacies, with the intent that improved access to the pharmacist will lead to an increase in patient interaction and pharmacist-assisted self-care. In this type of practice model, pharmacy technicians must play an enhanced support role in the areas of prescription preparation and insurance claim management to free up the pharmacist's time for patients. Pharmacy technicians have experienced growth in their training and credentialing that better prepares them to assist the pharmacist in a patient care-focused practice: The Pharmacy Technician Certification Board (PTCB) national certification examination is an example. Pharmacy technicians can screen patients to determine who needs to speak with the pharmacist, to assist patients in locating products in the pharmacy aisles, and to help with collecting data from patients, as well as with documentation and billing. Utilizing a new pharmacy layout; enhanced training; and improved teamwork to standardize, validate, promote, and expand the pharmacist's role in patient care will drive the pharmacists' availability and capability for a growing role in self-care.

Table 1-3 Minor Ailments Included in the NACDS Institute Study: Expanding Pharmacy Care—Innovative Models from the United States and Abroad

Bronchospasm, wheezing, shortness of breath from asthma or COPD	Acute otitis media	Conjunctivitis	Eye or nasal symptoms from seasonal allergies or other allergic conditions
Nausea and vomiting (not related to motion sickness)	Ear infections caused by bacteria	Migraine headaches	Anaphylactic allergic reactions
Nausea and vomiting caused by motion sickness	Lacerations and abrasions	Contraceptive pregnancy prevention	Allergic reactions from bee stings (not anaphylactic)
Herpesvirus infections (cold sores, genital herpes, shingles)	Wound infections from burns	Vaginal yeast infections	Diarrhea that occurs while traveling
Streptococcal pharyngitis	Animal bite (human, dog, or cat)	Uncomplicated urinary tract infections	Lack of fluoride for oral health

Key: COPD = Chronic obstructive pulmonary disease; NACDS = National Association of

Chain Drug Stores.

Source: Adapted from reference 30.

The Current Self-Care Marketplace

Consumers have access to and can purchase many health care products for self-medication. Three general categories of products are available for self-medication: (1) nonprescription medications, (2) dietary supplements, and (3) other products specific for complementary and integrative health therapies and approaches. [Chapter 4](#) provides details on the regulatory process for nonprescription medications. [Chapter 50](#) covers dietary supplements and natural products, and [Chapter 52](#) covers complementary and integrative medicine.

Nonprescription Medications

The nonprescription drug market represents about \$40 billion, or 60%, of the total pharmaceutical volume (units or number of packages) sold in the United States. [Figure 1–6](#) illustrates the details.³² Five product categories account for nearly 68% of sales in the nonprescription medications market: respiratory, oral care, gastrointestinal, internal analgesics, and antiperspirants ([Figure 1–7](#)). The estimated number of available U.S. Food and Drug Administration (FDA)-approved nonprescription drug products is well over 100,000, including more than 400 active ingredients that cover more than 700 therapeutic uses. The CHPA publication *Your Health at Hand Book: Guide to OTC Active Ingredients in the United States* provides an extensive list of active ingredients, therapeutic categories, and examples of trade-name products.³³

Figure 1–6 Breakdown of total U.S. pharmaceutical sales, by market classification. (Source: [Reference 32.](#)) Key: OTC = Over-the-counter; Rx = prescription.

Figure 1–7 Top-selling categories of nonprescription medications. Key: CCSF = Cough/cold/sinus/flu; OTC = over-the-counter. (Source: [Reference 32.](#))

Many nonprescription medications were once available only by prescription. A generally favorable environment for reclassification of prescription products to nonprescription status (Rx-to-OTC switch) in the United States has resulted in the availability of more than 700 nonprescription products today that were once available only by prescription. [Chapter 4](#) provides an in-depth discussion of Rx-to-OTC switches.

Dietary Supplements

A study conducted in 2018 by the Council for Responsible Nutrition found that 75% of Americans take dietary supplements, up from 65% in 2009.³⁴ Combination vitamin and mineral products remain the most popular dietary supplements, followed by singleingredient vitamin D, vitamin C, and calcium products. Herbs and botanicals, along with protein and energy supplements, also remain very popular. In the specialty supplements category, fish oil and probiotics continue to see strong sales, with probiotics estimated to reach \$2.6 billion in sales by 2020 (see [Chapter 20](#)). The overall dietary supplement market sales were \$43.2 billion in 2017, representing an all-time high.³⁵

Complementary and Integrative Health Therapies

Factors such as high out-of-pocket health care costs and restricted access to conventional health care providers lead some patients to seek care from complementary and integrative health providers. The National Center for Complementary and Integrative Health (formerly the National Center for Complementary and Alternative Medicine) reported in the 2012 National Health Interview Survey that 33.2% of U.S. adults and 11.6% of U.S. children used some form of complementary health care in 2012; similar results were reported in 2007.³⁶ The organization defines *complementary approach* as combining a non-mainstream practice with conventional medicine. Also, as in past surveys, natural products (nonvitamin and nonmineral dietary supplements) were the most commonly used complementary supplements. The mind-body approaches most commonly used by adults include yoga, chiropractic or

osteopathic manipulation, meditation, and massage therapy.³⁶

Wellness is the primary reason reported by users of natural product supplements or persons who practice yoga. Data on use of natural product supplements show that more than 85% of U.S. adults report using them for wellness, whereas more than 40% use them for treating a specific condition. More than 90% of U.S. adults who practice yoga do so for wellness, whereas more than 15% practice yoga to treat a health condition. More than two thirds of U.S. adults report feeling better from using complementary approaches.³⁶ The pharmacist is ideally situated to advise patients on appropriate choices of complementary and integrative health options. Advising patients on the best approaches requires integrating an understanding of pharmaceutical and natural product ingredients, physiology, pharmacology, potential interactions, and consumer behavior.

Legislative and Regulatory Issues Affecting Self-Care

The self-care environment is shaped by ongoing legislative and regulatory activities. Although a few unique issues are discussed here, details of the regulatory framework for nonprescription medications are provided in [Chapter 4](#).

The basic framework has been in place for decades; however, various state and federal legislative activities have an impact on access to and availability of these nonprescription medications. At the federal level, the use of flexible spending accounts that allowed consumers to use pretax dollars to purchase nonprescription medications was disallowed in 2011 as Congress sought ways to pay for the Affordable Care Act. Legislative efforts to restore this tax-incentivized opportunity are ongoing. At the state level, various legislative actions have addressed many areas relevant to nonprescription medications, including environmental impact (e.g., mandatory drug take-back programs, elimination of plastic microbeads from toothpastes and lotions), and pharmacist provider status and pharmacist prescribing authority (e.g., oral contraceptives, naloxone), which are discussed in [Chapter 4](#).

Concerns about pharmaceuticals in the environment have led individual states

to pass laws requiring manufacturer-funded take-back programs for drug disposal. Washington, California, and New York have enacted such legislation. In Illinois, Indiana, and Wisconsin, the presence of plastic microbeads in lakes led to the passage of laws that ban their use. Subsequently, a federal law that provides a harmonized timeline to ban the use of plastic microbeads in nonprescription medications and personal care products was passed in December 2015.

Educating the Public About Safe Medication Use: Collaborations

It is well known that education is an important component of any program to improve the safe and responsible use of medications. In addition, broad public education can lead to consumer empowerment, resulting in consumers' proactive management of their self-care for health and wellness. Education efforts require people, time, and money. Collaborations between a broad range of stakeholder groups, including health care professionals, government, academia, and industry, can achieve results that are difficult or impossible for one group acting alone. Such collaborations constitute an efficient way to utilize unique skill sets to develop and disseminate educational materials and messages to consumers through a variety of media. Impressive public-private partnerships have been formed to educate consumers on the safe use of nonprescription medications. Four such partnerships, described next, show that pharmacists are important stakeholders in the development and deployment of educational programming.

Be MedWise and Boy Scouts of America

A partnership between Be MedWise, a NeedyMeds (formerly National Council on Patient Information and Education [NCPPIE]) program, and the Boy Scouts of America provides Boy Scouts and Venturers ages 11–17 years with the opportunity to earn an achievement patch (see the [Color Plates](#), photograph 3) after completing four lessons on safe and responsible nonprescription medication use. The SCOUTStrong Be MedWise Award program teaches participating youths how prescription and nonprescription medications are alike and how they differ, as well as how to use nonprescription medications safely.³⁷

Up and Away

The message of the Up and Away campaign is to put medications “up and away”—that is, out of sight and reach of young children³⁸ (see the [Color Plates](#), photograph 4). Led by CDC, this innovative collaboration brings together public health agencies, private sector companies, professional organizations (including the American Pharmacists Association), consumer and patient advocates, and academic experts to develop strategies to keep children safe from unintentional medication overdoses. The developed messages are based on data and consumer research, and campaign partners work to expand the reach of these messages via social media, in-store materials, and in-office materials. Since 2011, emergency department visits for unsupervised pediatric medication exposures have dropped 3.4% each year, suggesting an incrementally positive impact of this educational effort.³⁹ Up and Away provides free educational materials on its website (www.upandaway.org/).³⁸

Know Your Dose

The Know Your Dose campaign was developed and launched in 2011 by the Acetaminophen Awareness Coalition (AAC), which consists of leading health, health care provider, and consumer organizations. The coalition’s goal is to educate consumers and patients on the importance of knowing the ingredients in their medications and following labeled directions to prevent unintentional acetaminophen overdose. Through outreach to health care providers, patients, and consumers, AAC works to ensure that acetaminophen is used only as directed or labeled. Partner organizations are diverse and include retailers, pharmacists (e.g., American Association of Colleges of Pharmacy, American Pharmacists Association), patient advocacy groups, and other health care practitioner groups. CDC, FDA, and the American Academy of Pediatrics are advisors to the coalition. The Know Your Dose campaign educates consumers and patients on how to use acetaminophen-containing medications safely. Materials are available for distribution to consumers and patients.⁴⁰ Although it can be difficult to measure the impact of educational campaigns, data from poison control centers show that since 2008, adult exposures to nonprescription acetaminophen combination products have decreased 30.4%⁴¹ (www.knowyourdose.org/).

OTC Medicine Safety Campaign

The APhA Academy of Student Pharmacists (APhA-ASP) partnered with McNeil Consumer Healthcare and Scholastic on the OTC Medicine Safety Campaign to teach the safe use and storage of nonprescription medications to 5th- and 6th-grade students and their parents or caregivers. This campaign is an opportunity for pharmacists and student pharmacists, working through APhA-ASP chapters at colleges of pharmacy, to educate participants about reading medication directions, the importance of following nonprescription label directions, proper measurement of a medication, safe storage and disposal of a medication, and the importance of consulting a parent or guardian before taking medications. Ready-made resources, including E-books, posters, and handouts designed to appeal to 5th and 6th graders, are available through the APhA-ASP website (www.pharmacist.com/apha-asp-otc-medicine-safety).⁴²

The Future of Self-Care: A Changing Marketplace and Advancements in Technology

Expansion of the Self-Care Marketplace

The self-care marketplace is expected to continue to grow, with more and improved medications and other consumer health care products available to consumers, particularly via community pharmacies. The pharmacist is playing an ever-increasing and influential provider role in assisting patients with self-care. Today, pharmacies offer vaccines and limited diagnostic testing. They also control access to medications such as pseudoephedrine to prevent abuse. In the future, pharmacists can be expected to administer more rapid diagnostic tests and to play a key role in disease identification, tracking, and management. More pharmacists will be prescribing medications such as oral contraceptives and naloxone as additional states pass legislation to improve the accessibility of these medications. The increased utilization of electronic medical record (EMR) systems is allowing more information to be shared by members of the health professional team, including pharmacists. Eventually, community pharmacists will be able to both review a patient's medical and

laboratory information and also enter important information from their self-care interventions into the patient's EMR.

For a pharmacist's self-care activities to expand, their integration into the workflow of pharmacy operations must be addressed. Workflow challenges currently exist with the delivery of patient care services such as immunizations. Any processes established to meet these challenges can be reapplied to self-care and other patient care services. A supportive financial infrastructure that allows compensation for patient care services also is crucial to sustain and build patient care practices in pharmacy. Passage of pharmacist provider status legislation mentioned earlier and new financial models of payment for pharmacists' patient care services will help address this opportunity. These changes position the pharmacist to play an ever-increasing and influential provider role in the self-care arena.

Technology

For those consumers interested in taking advantage of innovations, technology is enabling and redefining self-care in many ways, but differences among the various demographic groups must be considered. Older, less educated, and poorer Americans are much less likely to have online access.⁴³ For example, 10% of adults ages 18–29 said they do not use the internet in 2019, but that number increases to 27% among adults aged 65 and older. Yet 77% of Americans own a smartphone, and reliance on smartphones for internet access is especially common among younger adults, non-whites, and lower-income Americans.⁴⁴

In the past few years, consumer use of health monitoring technology has undergone tremendous growth. Applications available to smartphone users provide health monitoring, exercise tracking, dietary intake analysis, symptom analysis, and many more services. Wearable devices such as Fitbit and Apple Watch can provide feedback on physical fitness, quality of sleep, water intake, and even more health parameters. This collection of consumer health data can be a valuable aid in monitoring outcomes of treatment and lifestyle changes to improve health.

Nonprescription medications and dietary supplement products have also benefited from technology. Product package labels that contain QR codes (matrix barcodes) can provide much more information than that usually

printed on a standard Drug Facts label. The consumer simply uses the smartphone app to read the QR code to gain access to the additional content. One significant benefit is that these codes can hold multilingual labeling, which allows people in a region where different languages are spoken to use the same product and yet receive labeling information in their preferred language. Technology also has facilitated development of new dosage forms. For example, with application of such technology in producing chewable products, more pleasing dosage forms, such as chewable tablets and gummies, have become available. Rapid-release technology now is used in the manufacture of many nonprescription medications, such as instant-dissolve tablets or melting strips, which can make dosing for children more pleasant. Dosage form features also can offer a safety benefit, such as the flow restrictors in children's liquid acetaminophen products that provide a safeguard against accidental overdose.

The role of technology in health care will continue to expand, particularly in ways to actively engage consumers. Devices to allow point-of-care testing in the pharmacy as well as home monitoring techniques will continue to expand. For example, DNA testing for pharmacogenomic analysis to address appropriate medication use and the risk of certain diseases is becoming more widely available to the general public; this technology includes options that involve the pharmacist. For more information about the future vision of diagnostic testing by consumers, see [Chapter 48](#), and view the TED Talk video by Daniel Kraft, MD, who explores the impact and potential of rapidly developing technologies as applied to health and medicine.⁴⁵

Roles for the Pharmacist and Student Pharmacist in Self-Care Practice

As noted earlier, the role of the pharmacist has been slowly evolving from primarily dispensing medications to a health care provider role of improving medication use and health outcomes for patients. A combination of factors, including advanced education, better pharmacy layout, and favorable financial models, are supporting this practice change. With their ongoing development, student pharmacists also can be expected to play increasingly important roles in assisting patients with self-care needs. During their early professional shadowing experiences or introductory pharmacy practice experiences,

student pharmacists can observe the techniques used by the pharmacist to gather information, assess the patient, and provide recommendations. Later, during internships and advanced pharmacy practice experiences, student pharmacists can begin to engage in patient care. Under the supervision of their pharmacist preceptor, students can obtain initial basic information from the patient, help patients find products in the aisles, and later provide patient assessment and counseling. Student pharmacists can apply the specific information outlined in this section to help them develop patient care skills as they progress through their professional educational program.

Although patient counseling commonly occurs in the product aisle or at the pharmacy counter, utilization of private or semiprivate counseling areas is increasing, particularly for more extensive conversations. In the area of self-care practice, the pharmacist has the expertise to screen the patient's health information and apply professional knowledge and training to select products according to that patient's health care needs (see [Chapter 2](#) for further detail). A 2015 APhA survey of pharmacists reported on the critical role that pharmacists play in supporting patient-initiated self-care.⁴⁶ The 394 respondents reported that they provide patient counseling on self-care topics or nonprescription medications an average of 7.2 times each day. They also stated that patients were highly likely to select products consistent with their recommendations. The pharmacists identified the following areas as the most frequent counseling topics:

- Product selection for specific symptoms: 90%
- Potential drug interactions with other medications (prescription and nonprescription): 37%
- Dosing and administration information: 34%
- Signs and/or symptoms that indicate when to seek medical advice: 22%
- Side effects and safety considerations: 14%

The same pharmacists reported that patients most frequently requested assistance for the following self-care therapeutic areas:

- Cough and cold: 87%
- Seasonal and environmental allergies: 53%
- Gastrointestinal complaints: 28%
- Dermatologic conditions: 14%
- Dietary supplements: 11%
- Nicotine replacement therapy: 2%

In providing pharmacist-assisted self-care support, two key elements, efficacy and safety, are paramount considerations. First, the pharmacist must ensure that the medication selected is the most efficacious, taking into consideration the patient's unique needs and factors such as concurrent diseases, current medication use, lifestyle, daily routine, personal priorities and preferences, and desired outcome. The second key area of importance is ensuring the patient's safety by addressing many of the concerns and possible problems related to recommended treatments for the presenting complaint, to minimize the potential for harm. Possible areas of concern and higher risk for safety issues are addressed. In addition to safety and efficacy, consideration of treatment cost also should be reviewed with the patient. It also is critical to ensure patient confidentiality in addressing all self-care issues. Specific to product selection, when considering a medication's efficacy, the pharmacist must first help in identifying the best ingredient and dose for the patient based on the desired outcome. However, other factors can come into play. The dosage form of the product is an important factor to consider and must meet the needs of the patient. For example, pharmacists can work to enhance adherence and improve outcomes by selecting a coated tablet that is easier for an elderly patient to swallow or by recommending an extended-release formulation that requires fewer daily doses for a patient with a busy schedule. Cultural considerations must always be evaluated to ensure that patients' needs are met. More information on this topic can be found in [Chapter 3](#).

After helping a patient find the most efficacious medication, the pharmacist also should ascertain other ways to improve the patient's health or help manage a symptomatic condition. Recommendations could include lifestyle, dietary, and behavioral changes that will improve the patient's symptoms, contribute to optimal management for an underlying condition, or help prevent the development of other illnesses. Sometimes such recommendations become more important in ensuring the patient's wellness than the medication itself. For example, coaching patients with heartburn on dietary modifications may help prevent worsening of symptoms or progression to a more serious problem.

In addition to efficacy, medication safety is the other paramount concern of the pharmacist. Pharmacists must ensure that their patients understand all aspects of the self-care intervention, including the recommended medication dosage and special administration instructions. This step can be especially important for patients with limited health literacy. A critical counseling point is

ensuring that the patient knows the time limit for symptomatic improvement or, alternatively, if symptoms worsen, at what point to seek medical care. In the previously mentioned survey, pharmacists reported the following three top barriers to patient engagement for self-care⁴⁵:

- Patient is seeking recommendation of when medical care is indicated: 66%
- Patients are in a hurry to leave the pharmacy: 65%
- Patients erroneously consider nonprescription products to be overly safe: 64%

The pharmacist must play a key role in helping the patient understand safety parameters for self-care for a specific condition.

Pharmacists also must consider the needs of various special populations, including children and the elderly, patients who are pregnant or breastfeeding, and persons with chronic conditions. With patients who are pregnant or breastfeeding, self-care support is particularly challenging, because it is critical to balance the need for medication with the risk to their unborn child or infant. When possible, nonpharmacologic therapy should be the first option. Pharmacists are trained to assess whether a nonprescription medication is safe for use during pregnancy, yet women often make these decisions independently. The pharmacist can use FDA guidance information, textbooks that provide guidance,⁴⁷ and the primary literature to fully assess the potential risks and benefits of a patient's medication choices. Pregnant and breastfeeding patients always should be counseled about potential side effects that could occur in the child.

Elderly patients, with their reduced hepatic and renal function, decreased metabolism and muscle mass, heightened medication sensitivity, multiple disease states, and chronic medication use, constitute another group for whom special attention to benefits and risks is warranted. A study focused on this age group characterized the changes in medication and dietary supplement use from 2005–2006 to 2010–2011 in 2351 participants with mean ages of 70.9 years and 71.4 years for the two sampling periods, respectively.⁴⁸ The prevalence of prescription medication use, polypharmacy (concurrent use of five or more prescription medications), and use of dietary supplements increased whereas use of nonprescription medications declined during the 5-year span of the study. The use of interacting medications also increased over this period, highlighting the need for all health care providers to reinforce

safe use of medications in this population. Use of the Beers Criteria, along with numerous other sources, can be helpful in assessing the risks of nonprescription medication use in the senior population. ⁴⁹

Patients with chronic conditions also merit special attention before a product is recommended. For example, patients with chronic kidney disease can be at risk for further kidney damage with chronic exposure to nonsteroidal anti-inflammatory drugs.⁵⁰ Chapters in this book that cover medical conditions include sections that address management of these special populations.

Key Points

- Self-care involves the full spectrum of care, including prevention and wellness, diagnosis and screening, and treatment or relief of symptoms.
- Self-care is becoming more significant in today's health care systems because of numerous factors. Patients are becoming more accountable and focused on improving their health. Health care reform, combined with cost reduction pressures, is driving changes in health insurance and financial models as well as health care delivery that are all leading to increased use of self-care.
- Both health care providers and patients recognize the value and cost savings that self-care and nonprescription products provide to the health care delivery model.
- Consumers are utilizing the internet and other sources to increase their knowledge about self-care and available nonprescription products. The pharmacist continues to serve as a key resource to aid patients in assessing their condition and selecting appropriate self-care treatments.
- The changing demographics of the U.S. population, to include a greater number of older adults and non-Hispanic Whites and a large population with a low level of health literacy, requires health care providers to make special considerations for the self-care needs of these patients.

- The pharmacist's role is changing from prescription dispenser to patient care provider, allowing an enhanced role in assisting patients with their self-care needs. The newly established PPCP and the core elements of MTM are applicable in the pharmacist's role in assisting with management of the use of prescription and nonprescription medications.
- The estimated number of nonprescription drug products is already well over 100,000, and the self-care marketplace continues to grow. Fueling this growth is an expanding number of Rx-to-OTC switches and changes in state regulations to allow increased access to prescription products without a prescription.
- Pharmacists' education and training prepare them to play a key role in advising patients on self-care. In addition, pharmacists can provide broad public education on selfcare topics through numerous outreach programs.
- The future of self-care is predicted to continue to expand, with advances in technology, products, and devices and expansion of the role of the pharmacist.
- The pharmacist must emphasize efficacy and safety in assisting patients with their self-care needs. Special attention is needed for higher risk populations, including children, the elderly, pregnant and breastfeeding women, and persons with chronic conditions.
- Student pharmacists can build their self-care support skills as they progress through a pharmacy program—from early shadowing and introductory pharmacy practice experiences to internships and advanced pharmacy practice experiences.

Chapter 2: Pharmacists' Patient Care Process in Self-Care

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Pharmacists, and student pharmacists with appropriate supervision and mentoring, can play a valuable role in ensuring that medications are used safely and effectively in patients seeking self-care for a wide range of conditions. As discussed in [Chapter 1](#), the pharmacist can assist patients with identification of the clinical problem, selection of appropriate therapy, and/or referral to other health care providers, as needed. The pharmacist's involvement in the self-care process also may avert medication safety problems, such as duplicative therapy, drug interactions, or adverse drug reactions.¹⁻³ Community pharmacists currently have an active role in counseling patients about nonprescription medications and strongly believe that making nonprescription recommendations is an important part of their everyday practice.^{4,5}

The profession of pharmacy continues to evolve, from a primary focus on medication distribution to more advanced clinical decision making. Accordingly, the use of a systematic method or process to arrive at such decisions is desirable.^{6,7} A standardized process can be expected to ensure consistency in delivery of services to patients, including self-care encounters.⁸

The pharmaceutical care model developed by Hepler and Strand in the 1990s is one of the original systematic clinical practice blueprints for pharmacists.⁹ Other methods and approaches to providing pharmaceutical care, patient assessment, and medication therapy management have been developed, expanded, and used throughout the years; however, the types and levels of pharmacist-provided services vary between these models.¹⁰⁻¹⁴ This variation resulted in individual pharmacists' needing to determine the best model to use in a given situation. In 2014, the Joint Commission of Pharmacy Practitioners (JCPP) released the Pharmacists' Patient Care Process (PPCP), a contemporary, consistent, and comprehensive process. The PPCP is applicable to all areas of pharmacy practice and is built on previous approaches to care.⁸ Although this chapter guides the pharmacist in the use of the profession's uniform process to manage a patient's self-care disorders, other health care providers would use their own discipline-specific process to resolve a patient's

self-care concern.

Pharmacists' Patient Care Process (PPCP)

JCPP adopted a vision statement in November 2013 for pharmacy practice that states “patients achieve optimal health and medication outcomes with pharmacists as essential and accountable providers within patient-centered, team-based healthcare.”¹⁵ Recognition of the need for development of a uniform patient care process was an essential step toward achieving this vision of pharmacy practice.⁸

The PPCP is the result of a unified pharmacy professions' effort, supported by 13 national pharmacy organizations. It has been incorporated into Key Element 10.8 of the Accreditation Council for Pharmacy Education Standards 2016,¹⁶ thereby ensuring that a consistent process also is taught to student pharmacists. Implementation of the process into current practice settings is occurring through strategies that include, but are not limited to, the Pharmacy Health Information Technology Collaborative; the American Society of Health-System Pharmacists Accreditation Standards for Postgraduate Year One residency programs; and other various training programs, projects, and outreach activities.⁸

The PPCP is grounded in a patient-centered care approach that “is applicable to any practice setting where pharmacists provide patient care and for any patient care service provided by pharmacists.”⁸ For example, this process is just as applicable for the pharmacist working in a community-based or clinic-based ambulatory care setting as it is for the pharmacy professional embedded in an acute care health system. Similarly, this same process should be used when pharmacists provide patient care in a self-care encounter in a community pharmacy. The differences lie with the level of intensity in each step of the process based on the service provided.⁸

The five core components of the PPCP revolve around patient-centered care and the pharmacist's continual collaboration, documentation, and communication with prescribers, other pharmacists, and other health care providers (see [Color Plates](#), photograph 2).⁸ These five components are:

1. Collect

2. Assess
3. Plan
4. Implement
5. Follow-up: Monitor and Evaluate

PPCP in Self-Care: The Five Steps

Details about each key component of the PPCP and their implementation in patient care services are available in other published resources.¹⁷ Presented here is a brief summary of the five areas of the process, with emphasis on practical application in patient–provider interactions. Examples of how to apply the PPCP steps in specific self-care encounters are provided. These examples are intended to be snapshots of the patient encounter as a whole, rather than comprehensive procedural accounts. Diverse patient-specific factors may result in an assessment or plan for a patient, disorder, or symptom that differs from the general approach described in this chapter. The disorder-specific chapters in this book provide important background information of relevance, with referenced sources for further detail as desired, to allow the health care provider to fully research the disorder before engaging in a patient encounter. When applicable, Cases 2–1 through 2–4 are cited as examples of how to use the PPCP in self-care encounters; these cases are presented at the end of the chapter.

Step 1: Collect

“The pharmacist assures the collection of the necessary subjective and objective information about the patient in order to understand the relevant medical/medication history and clinical status of the patient.”⁸

Self-care encounters in community pharmacies generally are initiated in either of two ways: (1) either the patient or caregiver approaches or contacts the pharmacist, or (2) the pharmacist observes the patient or caregiver perusing nonprescription products on the shelf and offers assistance.¹⁸ A survey of practicing pharmacists reported that patients initiate the encounter 87% of the time.¹⁹ In either situation, the pharmacist must then engage the patient by collecting essential information to begin addressing the self-care complaint.

Collection of information from the patient or caregiver can be accomplished through the patient interview (subjective data) and by review of medical and

pharmacy records and reports of laboratory test results, direct observation, and physical assessment (objective data).²⁰ Subjective data generally are supplied by the patient or caregiver and may not always be accurate or reproducible. Conversely, objective data can be measured or observed and are not influenced by personal bias or emotion.²¹

A comprehensive patient interview will include the following components of the patient's health history^{18,20}:

- Chief complaint (CC)
- History of present illness (HPI)
- Past medical history (PMH)
- Health maintenance and immunizations
- Family history (FH)
- Personal and social history (SH)
- Review of systems and physical examination (ROS and PE)
- Medication history

Most information acquired in a self-care encounter will be subjective data obtained through the patient interview. The remainder of this information consists of objective data, collected by various means and from different sources. Of note, however, even objective data may not be entirely reliable. For example, the pharmacy record may indicate that a patient is taking one or more medications, but in fact the patient may not be adherent to the prescribed regimen. Such considerations require the pharmacist to confirm data in records with the patient—a clinical skill applied smoothly and efficiently with practice. Depending on the specific clinical situation, physical assessment skills also may be employed, such as measuring blood pressure or taking a temperature. Patients who present with a dermatologic disorder will require careful inspection of the skin. Case 2–1 documents the pharmacist's physical examination of the affected area (under the “Characteristics” heading) to assess a bee sting. Physical assessment techniques that apply to specific disorders are highlighted in the text and/or tables in subsequent chapters of this book.

The amount and type of information collected for a self-care encounter will be different from those required for other patient care services that involve a greater breadth and depth of care, and such encounters likely will not require covering all areas of the health history or full physical assessment.¹⁷ For example, for a patient who inquires about nonprescription therapy for sunburn

relief, collection of the family history may not be necessary, but appropriate assessment will include the chief complaint, history of present illness, and past medical history, in addition to observation of the area of concern on the patient's skin (see [Chapter 41](#)). Alternatively, a family history of colon cancer would be important information to collect in a patient who is inquiring about self-care for an anorectal disorder (see [Chapter 17](#)). In each self-care situation, the pharmacist will need to decide which assessment factors are pertinent. This determination requires knowledge of various self-care disorders, and subsequent chapters in this book provide a pharmacy practice-focused resource on types of information to collect for specific self-care disorders.¹⁸

The PPCP explicitly identifies patient-centered factors for which data should be collected: patient lifestyle habits, preferences and beliefs, health and functional goals, and socioeconomic factors. Some chapters in this book include “Patient Factors” and “Patient Preferences” sections, which focus on the patient-centered areas for which data should be collected and addressed as a part of developing the plan for that specific disorder. Additionally, [Chapter 3](#) reviews the cultural aspects of self-care as important background information to guide health care provider assessments and addresses several key areas of the data collection step in this context, including but not limited to cultural ideals and beliefs, literacy, and health literacy.

Professionalism, interview proficiency, and interpersonal and communication skills are essential to obtaining effective subjective information.¹⁷ Conducting an efficient patient interview is a skill that develops with practice over time and involves asking appropriate questions and actively listening to the patient.¹⁸ Communication skills are the foundation of many parts of the PPCP and are discussed further on.

Step 2: Assess

“The pharmacist assesses the information collected and analyzes the clinical effects of the patient's therapy in the context of the patient's overall health goals in order to identify and prioritize problems and achieve optimal care.”⁸

The second step involves the assessment and analysis of information collected to identify and prioritize the patient's problem(s).¹⁷ This assessment step can be categorized into three areas: (1) medication assessment, (2) patient history and risk assessment, and (3) preventive care assessment.¹⁷ Similar to the

collection step, assessing the patient's information may be more focused during a self-care encounter than during a comprehensive medication review. Additionally, it may or may not involve all three of these categories of assessment.

Medication Assessment

Comprehensive medication assessment involves the analysis of each medication for appropriateness, effectiveness, safety, and adherence.⁸ Further assessment of medications includes identification and prioritization of medication-related problems²²:

- Unnecessary drug therapy
- Needs additional drug therapy
- Ineffective drug
- Dosage too low
- Adverse drug reaction
- Dosage too high
- Adherence

In a self-care encounter, the most likely medication-related problem is “needs additional drug therapy,” as patients are presenting with the intent to purchase a self-care medication to treat a disorder and may require a nonprescription medication for resolution. Other medication-related problems in self-care include but are not limited to “ineffective drug,” if a patient is using a self-care medication that is ineffective or is not producing the desired response, and “adverse drug reaction,” if the patient is attempting to provide self-care for a disorder or a symptom that is the result of use of another medication. The pharmacist's role in the medication assessment step for self-care is to use the information collected to make appropriate medication recommendations or changes to the medication care plan.¹⁷

In contrast with a comprehensive medication review, during which the pharmacist performs an assessment of all medications the patient is currently taking for appropriateness, effectiveness, safety, and adherence, a self-care encounter is more consistent with a targeted medication review. Generally, self-care encounters require quick assessments because of the generally transient nature of the interaction. Such encounters may be initiated in an aisle outside the pharmacy counter (e.g., the pharmacist observes the patient reading several product labels and offers assistance), by telephone (e.g., a

patient or caregiver calls for advice about an appropriate medication or dose), or at the point of sale (e.g., the patient selects a product and asks the pharmacist questions during its purchase), when interaction is necessarily time-limited. Time limitations do not excuse the pharmacist from key responsibilities in medication assessments, particularly for safety and efficacy. However, in self-care encounters, the PPCP assessment step can be modified to a more focused approach.

Although the self-care encounter may not include a comprehensive medication review, the pharmacist may have compelling reasons to consider all current medications before making a recommendation. For a patient experiencing musculoskeletal pain, for example, the pharmacist may consider making a recommendation for a nonsteroidal anti-inflammatory drug (NSAID). Before any such recommendation, however, it is essential to collect information from the patient's profile and interview regarding current NSAID use to assess for duplicate therapy, drug–drug interactions, or drug–disease interactions (see [Chapter 7](#)).

Another example of a more focused approach in self-care encounters is assessing the cause of the patient's presenting medical condition or symptom as a potential medication-related problem. For a patient with a chief complaint of dyspepsia, the patient's current medication profile should be reviewed to determine whether a prescribed or other medication is causing an adverse effect, such as the recent addition of an antibiotic to the drug regimen (see [Chapter 13](#)).

Patient History and Risk Assessment

The patient history and risk assessment includes health and functional status, risk factors, health data, cultural factors, health literacy, and access to medications or other aspects of care that could influence decisions on optimal medication regimens for the patient.^{8,17} With certain self-care disorders, the collection of key information about the patient's health history, such as health and functional status, could direct the pharmacist's assessment to a completely different area of focus. The pharmacist should determine whether a patient's disease state could be causing or contributing to the presenting self-care symptom or disorder. For example, if a patient has congestive heart failure (CHF) and is seeking self-care for relief of a cough, the assessment would most likely result in a medical referral, as preexisting CHF is an exclusion

for self-care (see [Chapter 12](#)). The patient may be experiencing an exacerbation of CHF that requires medical attention beyond that for self-care. Case 2–2 demonstrates how collection of information about the patient’s chronic disorder can affect the scope and focus of assessment.

Health literacy is an important consideration to ensure delivery of safe and effective patient-centered care (see [Chapter 3](#)). Health literacy is defined as “the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions.”²³ Although validated tools are available to assess health literacy, their implementation may not be feasible in each selfcare encounter.²⁴ A more practical approach is to apply health literacy universal precautions, which assumes that all patients may have difficulty comprehending health information and accessing services.²⁵ The pharmacist should communicate clearly with everyone involved in the care of the patient and confirm that the patient understands the recommendations.

Cultural factors and health beliefs must be considered in the self-care assessment (see [Chapter 3](#)). Health beliefs constitute an array of patient opinions, including ideas about what causes illness and how to treat or prevent it.²⁶ These beliefs vary in individual patients and are greatly influenced by culture. This variability in turn may influence the kind of treatment a patient prefers, such as conventional nonprescription medications or complementary and alternative products. If a patient preference is identified, the pharmacist can use this information toward development of a patient-centered self-care plan.

Preventive Care Assessment

Preventive care assessment is an important part of the comprehensive assessment of a patient in the PPCP.^{8,17} In a specific clinical encounter, the pharmacist may focus the preventive care assessment on only the presenting disorder or problem. For example, in a patient seeking relief from the pain of sunburn, the pharmacist may assess the need for future sunburn prevention and recommend a preventive care plan that includes use of a sunscreen (see [Chapter 39](#)). Other opportunities in preventive care assessment should be used when appropriate. For example, during influenza season, the pharmacist should assess influenza immunization status in each patient presenting for self-care assistance.

Exclusions for Self-Treatment

A unique component of the PPCP in self-care management is the assessment of appropriateness for self-treatment. Within the process, pharmacists should collect the pertinent information for the disorder or problem that would lead to an assessment conclusion of “inappropriate for self-treatment.” If the pharmacist determines that the patient is not a candidate for self-treatment, the medication-related problem may be that the patient “needs additional drug therapy,” but the therapy may require an assessment from another health care provider, resulting in treatment with a prescription medication. Another outcome that may result from an exclusion for self-care is that “no drug therapy problem exists.” If a patient presents with a disorder or injury that requires medical treatment or a procedure from another health care provider as opposed to medication therapy, the patient may not have a medication-related problem to resolve.²² Exclusions for self-treatment that also require referral to another health care provider may include but are not limited to the following situations:

- Symptom characteristics or other disorder factors are beyond the scope of self-treatment.
 - Example: Patient presents with the symptom of headache that has persisted for 10 days (see [Chapter 5](#)).
- Patient-specific factors preclude treatment with nonprescription medications.
 - Example: For an 8-year-old child with excessive or impacted cerumen, nonprescription pharmacologic therapy is not indicated, because the patient is younger than 12 years (see [Chapter 30](#)).
- The patient’s health status or history precludes self-treatment, even if a nonprescription medication is indicated for the disorder.
 - Example: A pregnant patient presents with musculoskeletal pain that has not been previously assessed and diagnosed by an appropriate health care provider (see [Chapter 7](#)).
- Nonprescription medications are not indicated for the disorder.
 - Example: A patient presents with “bug bites,” but the lesions are characteristic of scabies, which requires prescription therapy (see [Chapter 37](#)).

- Previous treatment with nonprescription medications was ineffective after an adequate trial.
 - Example: Heartburn symptoms persist after 2 weeks of treatment with a nonprescription proton pump inhibitor (see [Chapter 13](#)).

The pharmacist is responsible for knowing exclusions for self-treatment for presenting disorders or symptoms, and for collecting appropriate information that may result in this assessment. In most subsequent chapters, exclusions for self-treatment for one or more disorders are included in text discussion and algorithm(s). Cases 2–2 and 2–3 provide examples of patients who have exclusions for self-treatment.

Step 3: Plan

“The pharmacist develops an individualized patient-centered care plan, in collaboration with other health care professionals and the patient or caregiver that is evidence-based and cost-effective.”⁸

The self-care plan in the patient care process uses the information collected and assessed and generally will culminate in one or more of three general recommendations: (1) recommend self-care with pharmacologic, nonpharmacologic, and/or complementary/alternative products; (2) refer the patient to an appropriate health care provider for treatment; and/or (3) recommend self-care until another health care provider can be consulted. The detailed components within the plan should address four key areas: medication-related problems, goals of therapy, patient engagement, and care continuity in collaboration with other health care professionals and the patient or caregiver.⁸

Medication-Related Problems

The plan for the first key area, medication-related problems, generally results in the pharmacist’s recommending a therapeutic product, such as a nonprescription medication, to resolve the “needs additional drug therapy” problem. Pharmacists should use their knowledge of the medication properties and determine the safest and most cost-effective option while considering all of the patient-specific factors identified in the first step. These patient-specific and therapy-specific factors include but are not limited to age, gender, medication history, medical conditions, allergies, active and inactive ingredients, adverse effects, potential interactions, and efficacy. The

recommendation also should be patient-centered, taking into account, at a minimum, patient preferences for dosage forms and dosing regimens, cost, flavors, and previous medication experience. The Drug Facts label on U.S. Food and Drug Administration (FDA)-approved nonprescription medications, further described in [Chapter 4](#), includes essential information that should be reviewed with the patient as part of the self-care plan and including but not limited to warnings and directions.

Goals of Therapy

Establishing goals of therapy has been a mainstay of the original pharmaceutical care process and remains central to the self-care plan in the PPCP.^{8,27} Goals of therapy serve as endpoints to measure outcomes and include both practitioner and patient contributions. They should be realistic, observable, and measurable and should include the following three components: clinical parameters (signs and symptoms) and/or laboratory values; a desired value or observable change in the parameter; and a specific time frame in which the goal is to be met.²⁷

Clinical parameters should include evidence-based guidelines or standards, when available, such as frequency of symptoms with heartburn. In self-care encounters, the clinical parameter is likely to focus on resolution of the presenting sign or symptom, such as “alleviate the discomfort associated with fever” when an antipyretic is recommended (see [Chapter 6](#)). Alternatively, the clinical parameter may be a preventive measure. For example, in a patient who presents with vomiting and diarrhea, an oral rehydration solution may be recommended not only to restore hydration status but also to prevent progression to severe dehydration (see [Chapter 16](#)).

In setting the clinical parameter, the desired value or change in the parameter also should be addressed. The patient should understand whether the goal of therapy includes complete resolution of the presenting symptom, a reduction in symptom severity or frequency, or partial relief. For a presenting complaint of fever, this portion of the goal might be to “*completely* alleviate the symptoms of discomfort associated with fever.” The patient-centered perspective may help determine the validity of this goal. The patient may be seeking elimination of pain as opposed to pain reduction. The pharmacist can ask three questions to help establish patient-centered goals²⁷:

- “What would you like to achieve with your medications?”

- “What are your goals for this therapy?”
- “How do you feel about trying to achieve (*insert desired outcome*) with a new drug therapy?”

Finally, the time frame in which the goal is to be met is a critical element of the self-care plan. Patients should understand how quickly the goal is achieved. In the fever example, the complete goal of therapy including the time frame might be that “the patient’s discomfort associated with fever will be completely eliminated within 2 hours.” The pharmacist should establish the time frame using both disorder-specific factors, such as medication onset and duration of action and appropriate length of time for self-treatment, and patient-specific factors, such as the patient’s or caregiver’s expectations for symptom relief. Setting a time frame establishes clear expectations. Case 2–4 demonstrates the goal of therapy (see step 8d, “Expected time to onset of relief” and step 8e, “Degree of relief that can be reasonably expected”).

Patient Engagement

Engaging the patient in the planning step involves “education, empowerment, and self-management.”⁸ Because the clinical encounter is initiated by the patient with the expectation of self-treatment for the disorder, inclusion of the patient in this portion of the self-care process is essential, because it is the patient who will carry out the treatment plan on leaving the pharmacy. Every self-care encounter in which the pharmacist provides care should include educating the patient on the presenting disorder, nonpharmacologic measures, nonprescription medications, and when to seek medical attention. Subsequent disorder-specific chapters include a display box that outlines appropriate patient education for the self-care condition discussed.

The pharmacist needs to identify the medication-specific information that should be communicated to the patient by reviewing information on the Drug Facts label in addition to any other medication-related instructions for successful use and therapeutic outcomes. A key part of an effective plan is communicating the goal of therapy and empowering the patient by inclusion in patient-centered goal setting to ensure that patient expectations align with the pharmacist’s recommendation.

Education on nonpharmacologic recommendations should be included in the plan. Patients should be educated on nonpharmacologic therapy (which includes nondrug measures, lifestyle recommendations, and preventive

measures) for their disorders, along with the nonprescription medication education. When a nonpharmacologic measure is the only recommendation, patient counseling also should specify the rationale for why that was preferable to a nonprescription medication. In the case of a patient who is experiencing insomnia caused by overuse of the stimulant caffeine, the most appropriate recommendation may be to discontinue or reduce caffeine consumption, particularly in late evenings, with corresponding education on proper sleep hygiene (see [Chapter 46](#)). Furthermore, emphasizing the potential risk versus benefit of nonpharmacologic measures for certain disorders may help promote acceptance of the nondrug plan.

Care Continuity

Finally, the plan should include care continuity, which involves follow-up, referral, and transitions of care.^{8,17} The initial follow-up plan is based on the goal of therapy and advises the patient regarding what to do once the goal is met, what should occur if the goal is not met, and what steps to take if the patient's condition worsens or the patient experiences an adverse effect. It should include the specific course of action to be taken and when that action is to be taken. The course of action may be a return to the pharmacist for further assessment, selection of a different nonprescription medication therapy, or referral to another health care professional, and it is essential to explicitly identify when that action is to be performed. If the patient has multiple goals of therapy, the follow-up plan should address each goal.

To further conceptualize the parts of the follow-up plan that should be addressed by the pharmacist in a self-care encounter, a series of questions is provided for consideration. Presented next is an illustrative case of a heartburn-related encounter, in which specific follow-up actions for the patient are suggested in response to each question.

Some preliminary notes are in order: In the following case, the pharmacist does not have a complete array of information including all patient-specific factors, and the example is not intended to serve as a plan for the management of all patients with heartburn. The follow-up plan will not be the same for each patient who presents with heartburn symptoms, and the pharmacist should refer to the disorder-specific chapters for more information. The pharmacist's responsibility is to recognize the disorder and know the limitations that would lead to a specific follow-up plan, including but not

limited to FDA-approved length of therapy for use of a nonprescription medication for self-care; common adverse effects associated with a nonprescription medication; developing or worsening symptoms that would lead to an exclusion for self-care, necessitating a medical referral; and appropriate stepwise use of an alternative nonprescription medication for efficacy.

In the example case, the patient presents with suspected heartburn (see [Chapter 13](#)). The pharmacist should evaluate the following:

- When the patient should expect results. This is communicated in the goal of therapy.
 - “Your heartburn symptom(s) should be completely gone within 10 minutes after taking the antacid.”
- What the patient should do if the goal of therapy is not met. For example, complete resolution of symptoms is the goal, but the time frame identified in the goal of therapy has passed and the patient sees no or only partial improvement. Options include the following:
 - A return visit to/communication with the pharmacist
 - “If your symptoms aren’t completely gone within 10 minutes, contact the pharmacist to help you select a different medication.”
 - Selection of a different nonprescription medication
 - “If your symptoms aren’t gone within 10 minutes, discontinue the antacid and begin omeprazole 20 mg once daily.”
 - Referral to primary care provider
 - “If your symptoms aren’t gone within 10 minutes, call your primary care provider for an appointment.”
- How long the disorder should be treated by self-care before further assessment by another health care provider (i.e., referral) is warranted
 - “If heartburn symptoms return after taking omeprazole for 14 days, as we discussed, call your primary care provider for an appointment.”
- What the patient should do (what action is indicated) in the event of an

adverse drug reaction.

- “If you develop diarrhea while taking omeprazole, stop taking the drug and call your primary care provider for an appointment.”
- What the patient should do if he or she experiences a worsening of the condition during the treatment
 - “If heartburn symptoms get worse or occur more often while taking this medication, call your primary care provider for an appointment.”

The pharmacist has the responsibility of identifying exclusions for self-care in the assessment step; therefore, the plan may not include any pharmacologic or nonpharmacologic recommendations. Each condition-specific chapter in this book identifies exclusions for self-care, usually within a treatment algorithm. The plan may simply be referral to another health care provider. Little is known about how often pharmacists make a medical referral in self-care encounters; however, a study of pharmacist consultation outcomes reported that a medical referral was made in 4.3% of the encounters.¹ Cases 2–2 and 2–3 provide examples of self-care situations leading to medical referrals.

Another unique component of self-care encounters is to recommend self-care until another health care provider can be consulted. The pharmacist typically is well positioned for this role in self-care management, simply because of ready access within a community pharmacy. The initial assessment may reveal that referral to another health care provider is warranted. If the situation is not urgent, however, the pharmacist may consider recommending self-care, pharmacologic or nonpharmacologic, while simultaneously referring the patient for further evaluation and treatment. For example, for a pediatric patient with signs of moderate dehydration, patient-specific factors identified in the initial assessment may raise concerns that the parent or caregiver may not be successful in preventing further dehydration using an oral rehydration solution. The pharmacist's recommendations may then include both referral for medical evaluation and initiation of oral rehydration, to slow the progression to severe dehydration until the patient can be seen by a medical provider (see [Chapter 16](#)). The risk in making a recommendation while waiting for an appropriate health care provider consultation is that the patient or caregiver may ignore the referral and take only the self-care recommendation. This risk is one reason why the follow-up action step with the patient is so

important in self-care practice.

The pharmacist must emphasize the importance of seeking further medical evaluation and clarify to the patient that the referral is the primary recommendation. To avoid patient denial and confusion, the pharmacist should provide clear and understandable instructions. For the preceding case example on oral rehydration solutions, appropriate instructions follow:

“Contact your primary care provider today and make an appointment. Ask for an appointment today or tomorrow morning, at the latest. In the meantime, use this oral rehydration solution as directed to help alleviate some of the symptoms. This will likely not be enough to prevent serious complications, so do not delay in contacting your primary care provider today.”²⁸ Follow-up with patients requiring referral is especially important to ensure that the situation has been properly addressed. Case 2–2 requires a plan for referral because the patient has an exclusion for self-care. Recommendations for some nonpharmacologic measures to use until the patient can see a primary care provider, however, are listed as well.

Step 4: Implement

“The pharmacist implements the care plan in collaboration with other health care professionals and the patient or caregiver.”⁸

The implementation step in PPCP is execution of the developed plan. Implementing the plan for medication-related problems would include selecting the recommended nonprescription medication from the pharmacy nonprescription section and presenting it to the patient. A full implementation step for self-care would not involve merely directing the patient to the respective aisle number to obtain the product. Implementation also includes communicating the “Goals of Therapy” that were established in the plan.

In the “Patient Engagement” part of the plan, all of the pharmacologic and nonpharmacologic educational points were established, and the implementation step is the actual provision of the education to the patient or caregiver. As with the collection step of the process, effective communication skills are required, taking into account health information collected from the initial assessment. In addition to health literacy, patients with low literacy may have difficulties comprehending information on the Drug Facts label, and additional counseling time may be required to ensure that they understand

the key concepts for appropriate use. Use of various communication methods, including but not limited to the teach-back method, may confirm that the patient understands the information. The teach-back method involves explaining the information and then asking the patient to repeat key points, and also to discuss the information as it applies to the medication regimen, and actively listening to ensure that the patient has achieved understanding.²⁹ Requesting patients to repeat the treatment information provided, in a nonjudgmental way, and supplying easy-to-read, patient-centered printed instructions have been shown to improve patient understanding and proper medication use.³⁰ Essential communication components are discussed later under “Patient-Centered Care.”

For “Care Continuity,” all of the follow-up components to the plan should be communicated to the patient and/or caregiver. If one of the follow-up actions includes returning for a follow-up visit within a specified time frame, the patient should be provided with a specific day or date on which the pharmacist will be available. Community pharmacists may have various shifts and schedules, so fully implementing the follow-up plan should include factors such as the pharmacist’s availability or formalizing an appointment. Follow-up encounters other than face-to-face meetings may be arranged, when appropriate, using telephone or other communication technologies such as email.

In self-care management, implementation may involve a referral to an appropriate health care provider or facility. The pharmacist may contact the patient’s primary care provider to communicate patient-specific information obtained during the self-care encounter, to facilitate the reason for referral. For those patients who do not have a primary care provider, the pharmacist may be integral in connecting the patient to an urgent or convenient care facility until a primary care provider contact can be established. In extreme cases, the pharmacist may call 911 in a medical emergency.

Step 5: Follow-up: Monitor and Evaluate

“The pharmacist monitors and evaluates the effectiveness of the care plan and modifies the plan in collaboration with other health care professionals and the patient or caregiver as needed.”⁸

Follow-up “brings the pharmacist full circle in the ongoing monitoring of the

patient.”¹⁷ Follow-up may not be a routine occurrence with most self-care encounters. Some literature suggests that patients may be willing to have a follow-up service for selfcare encounters.² However, because of the self-limiting nature of most presenting disorders in self-care, the pharmacist may not be included or choose not to be involved in the follow-up plan. For example, if the patient’s goal of therapy and follow-up plan include full relief of symptoms within 4 hours and resolution of the disorder within 10 days, and the goal is met, no further follow-up with the pharmacist may be warranted. Similarly, in follow-up plans that include a referral to the primary care provider, if the patient’s symptoms worsen or do not resolve, the follow-up step may not occur with the pharmacist.

If, however, the follow-up plan includes a return visit to the pharmacist within an identified time frame, the pharmacist should begin the PPCP evaluation again by collecting new information and reassessing the patient’s condition. The patient’s goal of therapy should be reviewed for achievement, and an assessment for appropriateness, efficacy, safety, and adherence of any new medication-related problems related to the recommended nonprescription medication is warranted. Adherence to recommended therapy should specifically be addressed in the follow-up step to determine its contribution to the success or failure of the intended outcome.

The pharmacist’s role in a follow-up encounter with the patient after medical referral can be challenging. A patient seeking self-care may not be an established patient at the pharmacy or with the pharmacist. The person may simply be seeking a consultation for the first time as a walk-in patient. Without a strong pharmacist-patient relationship, the logistics of following up with the patient to determine the outcome of the referral are difficult. The pharmacist may not have the essential demographic information often maintained in pharmacy records for these one-time encounters. Asking the patient for a phone number for a follow-up call may be a simple solution to initiating follow-up. For an established patient, a follow-up inquiry about the outcome of the referral brings closure to the entire PPCP. Future developments in transitions of care for established patients may help close the loop in the process. With access to electronic health records, for example, community pharmacists could communicate follow-up plans and medication changes for continued care.

PPCP in Self-Care: The Core

The PPCP has patient-centered care at its core, with continual collaboration, communication, and documentation of care with other health care providers (see [Color Plates](#), photograph 2).⁸ Developing the pharmacist–patient relationship helps establish engagement and effective communication with patients and/or caregivers to ensure that the process remains patient-centered. Presented next is an overview of the importance of patient-centered care in pharmacist patient care services, followed by detailed descriptions of each of the three core areas, with an emphasis on implementing these areas in the self-care encounter.

Patient-Centered Care

Patient-centered care, according to the Institute of Medicine (IOM), is defined as “providing care that is respectful of and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions.”³¹ IOM describes patient-centered care in greater detail in its 2001 report *Crossing the Quality Chasm: A New Health System for the 21st Century*. Each self-care encounter affords multiple opportunities to center the process on the patient.

The pharmacist must listen to the wants and needs of the patient when collecting information. Careful consideration of all relevant patient factors is essential to arrive at an assessment and plan that is truly patient-centered. Lifestyle habits, preferences, and beliefs, as previously described in the five steps, all are important patient-centered collection areas.

Establishing goals of therapy must include the patient’s input. Understanding the patient’s expectations of the desired outcome and time frame must be carefully considered in developing the plan. Furthermore, patient-centered implementation of the plan involves using collected patient factors regarding literacy, health literacy, and physical functions such as vision or hearing status to tailor the education and counseling to the patient’s specific needs.

An additional patient-centered area for consideration is the patient’s medication experience. The patient’s medication experience is “the sum of all the events a patient has in his [or her] lifetime that involved drug therapy. This is the patient’s personal experience with medications. This lived experience

shapes his attitudes, beliefs, and preferences about drug therapy.”³² In a brief self-care encounter, the pharmacist may focus on the patient’s personal experience with nonprescription medications or specific experiences with a certain self-care disorder. For example, if a patient expresses fear about taking a particular nonprescription medication because a family member had a bad experience with that drug, the patient’s concerns about drug safety can be recognized and addressed.³²

Specific Core Components

Collaborate

Collaboration involves working together to achieve a common goal. In self-care, collaboration occurs most often with patients and/or caregivers to ensure the entire process is patient-centered and optimal outcomes are achieved. Collaboration with other health care providers is less common in self-care encounters; however, it is essential when referrals are required or if more information is needed for safe and effective self-care recommendations.

Communicate

Although communication in the PPCP involves both providers and patients, most of the communication will be with patients in self-care encounters. Good communication skills are essential in all pharmacist interactions with patients and are not unique to self-care.

Fundamental communication skills, such as active listening and demonstrating empathy, must be mastered for collecting information.^{18,33} Active listening requires concentration and a focused effort to minimize external and internal distractions. Empathetic responses are a result of listening, and it is through empathetic response that patients feel understood.³³ Other essential communication skills include asking open-ended questions, avoiding leading questions, being aware of nonverbal modes of communication such as tone of voice or facial expression, and using the teach-back method.^{18,33}

Pharmacists need to use effective communication skills when faced with challenging situations in which patient and caregiver factors, such as vision and hearing loss, language barriers, and limited literacy and health literacy, may impede communication, and should know how to address these

challenges. Pharmacists' assumptions in resolving communication challenges may not always be appropriate. For example, with patients who are deaf or hard of hearing, the interviewing pharmacist should ask about their preferred method of communication, which may be written notes, lip reading, or the use of an interpreter, and should not assume that the same communication method applies in every patient.

Maintaining patient privacy and ensuring Health Insurance Portability and Accountability Act (HIPAA) compliance in communications for self-care encounters are important considerations, especially because the encounter initiation may occur in an open area of the pharmacy where nonprescription medications are located. Additionally, many self-care disorders include sensitive issues or topics that may be difficult or embarrassing for the patient to discuss, including but not limited to anorectal disorders, vaginal and vulvovaginal disorders, and prevention of pregnancy and sexually transmitted infections. Pharmacists must ensure that the consultation occurs at the appropriate place. Choosing a private area that minimizes interruption and provides a safe place for the patient to discuss his or her condition and health concerns is ideal. Being aware of voice volume to maintain confidentiality also is important. Using the foundational skills of active listening and empathy will further contribute to developing a trusting relationship that is needed for discussion of sensitive topics.³⁴

Document

Documenting pharmacist–patient encounters is an essential part of the PPCP. Documentation demonstrates the pharmacist's contributions to patient care, ensures continuity of care, provides legal evidence for professional liability, and contributes to billing and reimbursement needs. For these important reasons, pharmacists should document self-care encounters, whenever possible.

Documentation methods in community pharmacy vary. A survey of such methods revealed that community pharmacists who currently document patient care services use both paper (54%) and computerized (42%) documentation systems; however, little is known about documentation of self-care encounters.³⁵ Some sample paper documentation forms have been included and may serve as useful tools (Figures 2–1 and 2–2).^{28,36} Additionally, pharmacy management systems, typically designed for prescription medications, may have features that provide a venue for selfcare

documentation. Improved health information technology systems that fully integrate the PPCP steps may improve self-care documentation in community-based pharmacy.³⁷ Patient data and health information documented in a self-care encounter would be considered private information and protected under HIPAA.

FIGURE 2–1 Sample documentation form for pharmacist consultations for drug management using the QuEST/SCHOLAR-MAC and Pharmacists' Patient Care Process (PPCP) models. Key: OTC = Over-the-counter; RPh = Registered Pharmacist; Rx = prescription.

FIGURE 2–2 University of North Carolina School of Pharmacy self-care documentation form. Adapted from APhA *OTC Advisor: Advancing Patient Self-Care* Certificate Training Program and *Am J Pharm Ed* 2006;70(6): Article 142. Used with permission. For the main elements of these tools, the corresponding SOAP component is shown in parentheses. Key: SOAP = Subjective, Objective, Assess, Plan.

FIGURE 2–2 University of North Carolina School of Pharmacy self-care documentation form. Adapted from APhA *OTC Advisor: Advancing Patient Self-Care* Certificate Training Program and *Am J Pharm Ed* 2006;70(6): Article 142. Used with permission. For the main elements of these tools, the corresponding SOAP component is shown in parentheses. Key: SOAP = Subjective, Objective, Assess, Plan. (*continued*)

Efficient Use of PPCP in Self-Care

Efficiency in the PPCP is imperative in a community pharmacy. Self-care encounters are generally not compensated outside the sale of the product; thus, the pharmacist is faced with a time management decision.³⁸ Pharmacists identify lack of time as a barrier to their involvement in resolving

self-care needs in community pharmacies because of their responsibilities in medication distribution.⁵ The time pharmacists actually spend with patients or their perception of patients' time expectations for the entire selfcare interaction is in the range of 2–6 minutes.^{1,19,36,39} Patients also report an expectation that encounters are brief, indicating a willingness to spend 1–5 minutes for a nonprescription consultation.⁴⁰

Although time constraints are a reality in community practice, professional responsibilities lie with patient care, which includes all steps of the PPCP, from collecting all pertinent information to appropriately assessing the patient and completing, communicating, and implementing the plan.¹⁸ In the previous section's comprehensive overview of the PPCP, outlining each step within the process and the multiple components of each step, it was noted at each step where modifications may occur for patient care services in self-care encounters to improve efficiencies. Another way to increase efficiency in applying the PPCP in self-care is the use of algorithms or flow charts. Treatment algorithms developed for disorders discussed in this book focus on the most pertinent information to collect and assess within the patient care process for that particular disorder. The algorithms also assist with components of the planning step by identifying appropriate lengths of therapy and follow-up time frames as well as exclusion criteria.

QuEST/SCHOLAR-MAC

Tools, mechanisms, and mnemonics have been used in patient assessment in multidisciplinary health care professions for many years.^{20,41,42} Some mnemonics developed and used by pharmacists during assessments have been shown to improve assessment skills when implemented,^{43,44} whereas others have been used rather extensively yet never truly validated.

One tool designed specifically for self-care encounters, the QuEST/SCHOLAR method, was first presented by Leibowitz and Ginsburg at the 2002 Self-Care Institute of the American Pharmacists Association.⁴⁵ This method employs a simple acronym to prompt health care providers to complete key steps in the self-care problem-solving process. Although no published studies have compared QuEST/SCHOLAR with other tools or mnemonics or validated its use in patient outcomes, the easy-to-remember acronyms can be expected to expedite completion of the problemsolving process relative to more structured models that contain no such prompts. One study conducted in a school of

pharmacy concluded that utilizing QuEST in a skills-based course improved student pharmacists' ability to provide self-care counseling and elicit important patient information in a consistent manner.⁴²

Each letter in the QuEST mnemonic represents an ordered step in the problem-solving process⁴⁵:

- Quickly and accurately assess the patient (using the SCHOLAR-MAC interviewing tool described here).
- Establish that the patient is an appropriate self-care candidate.
- Suggest appropriate self-care strategies.
- Talk with the patient.

Similarly, each letter in the mnemonic SCHOLAR represents information that the health care provider should elicit from each patient or caregiver:

- Symptoms: What are the main and associated symptoms?
- Characteristics: What is the situation like? Is it changing?
- History: What has been done so far? Has this ever happened before, and, if so, what was done then? What was successful? What wasn't?
- Onset: When did it start?
- Location: Where is the problem?
- Aggravating factors: What makes it worse?
- Remitting factors: What makes it better?

The MAC component was added to the QuEST/SCHOLAR tool as a prompt for users to collect additional key medical history information:

- Medications: prescription and nonprescription as well as complementary and alternative products
- Allergies: to medications and other substances
- Conditions: coexisting health conditions

QuEST/SCHOLAR-MAC is not a new problem-solving model or a different process for patient care. It is one option to assist the pharmacist in streamlining the PPCP in self-care encounters by highlighting key areas within the process that are most relevant for self-care. Recognition of this purpose is important, because models and mnemonics may be misinterpreted as entirely new processes to apply instead of welcomed as tools to assist in learning and in making the existing process more efficient. [Figure 2–3](#) demonstrates the

relationship of the QuEST/SCHOLAR-MAC components to the PPCP steps. Additionally, Cases 2–1 and 2–3 illustrate the application of this tool in the PPCP.

FIGURE 2–3 Relationship between PPCP and QuEST/SCHOLAR-MAC patient assessment models. Key: OTC = Over-the-counter; PPCP = Pharmacists' Patient Care Process; Rx = prescription.

Special Populations and PPCP in Self-Care

Special considerations in the PPCP are warranted for certain groups of patients known to be at higher risk for medication-related problems. These populations include pediatric, geriatric, pregnant, and lactating patients, in whom medication-related problems with nonprescription products can have serious consequences, even in a self-care setting. This final section of the chapter summarizes the characteristics and physiologic and pharmacokinetic considerations for various special populations and provides general considerations for self-care encounters using the PPCP in each such patient group. Most disorder-specific chapters in this book include a “Special Populations” section under “Product Selection Guidelines.”

Pediatric Patients

Pediatric patients present unique challenges in providing selfcare recommendations. The pediatric population consists of the following subgroups: neonates (birth to 1 month), infants (1 month to 2 years), children (2–12 years), and adolescents (12–16 years).⁴⁶ Significant differences in the pharmacokinetic and pharmacodynamic profiles between the pediatric subpopulations and general adult profiles are well recognized.

Pharmacokinetic processes (e.g., absorption, distribution, metabolism and excretion) in the pediatric population vary widely because body and organ systems in this age group are in a continuous state of growth and development.⁴⁷ The body is less tolerant of changes, especially within the younger age spectrum, which includes neonates, infants, and children. Clinical data for pediatric patients are limited, resulting in insufficient drug labeling and potential challenges with medication dosing and administration.⁴⁸ With these patients, it is particularly important to carefully evaluate the basis for

self-care recommendations and to closely follow approved labeling recommendations when self-treatment is deemed appropriate. A further consideration is that the pharmacist will communicate with the parent or caregiver in most encounters, rather than directly with the patient, which may affect data collection and other aspects of the PPCP assessment in this population.

PPCP Considerations for Pediatric Patients

Specific information to consider during each step of the PPCP for pediatric patients is outlined next.

Collect

- Verify the patient's age.
 - Several nonprescription medications have exclusions for use based on age. For example, ibuprofen is not indicated in children younger than 6 months (see [Chapter 6](#)).
 - Age is an important predictor of general exclusions for self-care regardless of nonprescription product indication and labeling. For example, infants younger than 3 months who present with fever are not candidates for self-care management and should receive a medical referral (see [Chapter 6](#)).
 - Age also can help guide dosage form selection. In general, younger children (<6–7 years) may have difficulty swallowing solid oral dosage forms. However, this patient-specific factor varies by age and should be reviewed and assessed individually.⁴⁹
- Obtain the patient's weight.
 - Nonprescription medications may be dosed according to weight for infants and children. For example, acetaminophen is dosed at 10–15 mg/kg every 4–6 hours (see [Chapter 5](#)).
- Consider caregiver factors.
 - Collecting information that leads to an appropriate assessment of the literacy and/or health literacy of the parent or caregiver is important when that person will be implementing self-care measures for the pediatric patient.
- Consider potential child care or school scheduling.

- Collecting information on whether the child attends daycare or school or is involved in extracurricular activities may help guide product selection based on dosing frequency or ease of administration.

Assess

- Determine exclusions for self-treatment.
 - Pediatric patients are more likely to have exclusions for self-treatment for various reasons. Examples are circumstances for which nonprescription medications are not available for the child's age group or in which the disorder is not self-treatable because of age considerations. For example, girls younger than 12 years who present seeking treatment for vulvovaginal candidiasis should be referred to a pediatrician or other specialist. Referral is required because of the rarity of this condition in children, which may be indicative of a more serious disorder (see [Chapter 8](#)).
- Evaluate for potential adverse drug effects.
 - Some nonprescription medications have the potential to cause unique adverse effects in children that would not occur in adults. For example, some antihistamines may cause paradoxical effects or excitation in children (see [Chapter 11](#)). With this possibility in mind, the pharmacist may recommend giving the antihistamine earlier in the day to gauge response and monitor for a potential adverse reaction, or administering the first dose on a weekend to avoid negative effects on school performance.

Plan and Implement

- Consider nonpharmacologic therapy.
 - Recommendations for nonpharmacologic measures for selfcare may be more common for pediatric patients than for the general adult population because of labeling restrictions of nonprescription medications, safety issues, and/or unknown factors regarding the use of certain products in this age group. For example, FDA recommends that cough and cold products not be used in children younger than 2 years of age, requiring nonpharmacologic measures as the primary recommendation for

treating colds in younger pediatric patients⁵⁰ (see [Chapter 11](#)). Pharmacists should assess the need for nonpharmacologic interventions and educate the parent or caregiver when nonpharmacologic recommendations are made. Parents with older children or those who may have used cough and cold products before the FDA recommendations were made available may not be aware of the changes or understand the rationale. Research confirms that parents may be unaware of the FDA changes,⁵¹ may continue to use products despite awareness of the changes,⁵² and/or lack confidence in the FDA recommendations.⁵³ The pharmacist has an important role in educating parents and/or caregivers, for whom additional time may be needed for effective counseling.

- Provide specific patient education and counseling.
 - FDA and the Consumer Healthcare Products Association have extensive resources for parents and caregivers on selection, dosing, and administration of nonprescription medications to children.^{54,55} The pharmacist's familiarity with these resources may be beneficial in patient-specific communications and also with general educational opportunities within the pharmacy.
- Describe and demonstrate appropriate dosing and administration of medications.
 - Liquid formulations require accurate measuring to ensure appropriate doses are administered, and their use has historically been a source of medication errors and unintentional medication overdoses.⁵⁶ FDA released guidelines in May 2011 for liquid nonprescription medication products that include a requirement for packaging to include a product-specific dispensing device, such as a dropper, cup, oral liquid syringe, or calibrated spoon.⁵⁷ Parents and caregivers should be instructed to use only the device included with that particular product, and only for one patient/child. No standard was available before release of the guidelines, and almost all pediatric nonprescription liquid medications contained highly variable and inconsistent dosing directions and measuring devices.⁵⁸ [Table 2-1](#) summarizes the key points of the guidance document.
 - The American Academy of Pediatrics (AAP) published

recommendations in April 2015 that called for exclusive metric-based dosing (i.e., mL) to avoid dosing errors associated with common kitchen spoons (i.e., teaspoons, tablespoons). They include a call for manufacturers to eliminate labeling, instructions, and dosing devices that contain units other than metric units. To date, however, FDA has not made any changes based on these recommendations.⁵⁶ AAP encourages advanced counseling strategies (e.g., teach-back, drawings/pictures, dose demonstration, show-back) to further reduce dosing errors.⁵⁶ The pharmacist is uniquely qualified for this role in self-care support with use of oral liquid nonprescription medications for pediatric patients.

- Age-appropriate tips for oral liquid medication administration are provided in [Table 2-2](#).
- Consider engaging the child.
 - Depending on age, the pharmacist may wish to include the child in the implementation step by allowing handling of the administration device, demonstrating its use, describing the medicine's flavor or taste, explaining how the medicine makes people feel better, encouraging the child's participation through reminders to the parent/caregiver about dosing ("Time for my medicine!"), and emphasizing that medicine should be taken only when given by the parent/caregiver. To effectively involve the child, the pharmacist should get down on a physical level that allows speaking directly to the child.

Table 2-1 FDA Key Recommendations on Dosage Delivery Devices for Orally Ingested Nonprescription Liquid Drug Products

- A dosing device should be included with all oral liquid nonprescription products.
- The device should be calibrated to the dose recommended in the product directions (e.g., teaspoon, tablespoon, milliliter).
- The device should be used only with the product with which it is packaged.
- The markings should remain visible even when the liquid is in the device.

Key: FDA = U.S. Food and Drug Administration.

Source: Reference 57.

Table 2–2 Selected Administration Guidelines for Oral Medications

Infants

- Use a calibrated dropper or oral syringe.
- If a medicine dropper is used, the medication should be squirted into the side of the cheek and not straight back into the throat so that the infant does not choke.
- Do not place the child's medication in the formula, because the baby might not like the taste of the formula and might refuse to take this formula in the future.
- Support the infant's head while holding the infant in the lap.
- Give small amounts of medication at a time to prevent choking.
- Crush non-enteric-coated or non-sustained-release tablets into a powder and sprinkle them on small amounts of food, if infant has been introduced to solid foods.
- Provide physical comfort while administering medications to help calm the infant.

Toddlers

- Allow the toddler to choose a position in which to take the medication.
- If necessary, disguise the taste of the medication with a small volume of flavored drink or small amounts of food. A rinse with a flavored drink or water will help remove an unpleasant aftertaste.
- If the medication is not palatable, ask the pharmacist whether the pharmacy offers a flavoring service and can add flavoring to the child's medication. Refrigeration also may help.
- Make sure that the medication is not referred to as candy.
- Use simple commands in the toddler's jargon to obtain cooperation.
- Allow the toddler to choose which medication (if multiple) to take first.
- Provide verbal and tactile responses to promote cooperative taking of medication.
- Allow the toddler to become familiar with the oral dosing device.

Preschool Children

- If possible, place a tablet or capsule near the back of the child's tongue, then provide water or a flavored liquid to aid the swallowing of the medication.
- If the child's teeth are loose, do not use chewable tablets.
- Use a follow-up rinse with a flavored drink to help minimize any unpleasant medication aftertaste.
- Allow the child to help make decisions about dosage formulation, place of administration,

which medication to take first, and type of flavored drink to use.

Follow-up: Monitor and Evaluate

- Pharmacists should ensure that the parent or caregiver has a clear follow-up plan that specifies a specific time frame and appropriate action step. Because of pediatric patients’ smaller body mass and decreased physiologic tolerance to change, parents or caregivers may be directed to schedule a follow-up visit with another health care provider as soon as possible to avoid potential adverse events.

Geriatric Patients

The U.S. geriatric, or older adult, population, defined as that consisting of people 65 years of age and older, is growing rapidly, and its members are heavy consumers of both prescription and nonprescription medications, as discussed in [Chapter 1](#).^{59,60} Pharmacists can expect a large number of self-care requests and encounters for patients in this age group. Understanding the unique characteristics and needs of older adults is critical to achieving appropriate patient-centered care.

The aging process includes certain physiologic changes and decline in the function of many organ systems.⁶¹ A number of these changes and characteristics can affect pharmacokinetic and pharmacodynamic profiles of medications. Absorption, distribution, metabolism, and excretion, the four primary facets of *pharmacokinetics*, or how the body processes a drug, can be altered in older adults. The general age-related pharmacokinetic changes are well described in the literature and are summarized in [Table 2–3](#).^{59,62}

Table 2–3 General Age-Related Pharmacokinetic Changes in Older Adults	
Pharmacokinetics	Physiologic Change(s)
Absorption	Increased GI secretions and motility; decreased surface area and blood flow; increased pH
Distribution	Decreased total body water and muscle mass; increased body fat
Metabolism	Decreased hepatic blood flow and enzyme activity

Pharmacokinetics	Physiologic Change(s)
Elimination	Decreased renal function

Key: GI = Gastrointestinal.

Source: References 59 and 62.

The overall effect of changes to absorption, distribution, metabolism, and excretion varies, making it difficult to accurately predict the pharmacokinetic profile of a specific drug in older adults. Patients in this age group experience these changes to a variable degree or may not experience them at all. Without the ability to assess the individual patient's specific body functionality, the pharmacist may often assume that the older adult has age-related changes in function and then adjust medication and dosage recommendations accordingly. For example, if an older adult presents seeking advice for a nonprescription calcium supplement for bone health, the pharmacist may consider a recommendation for a calcium citrate product because it relies less on gastric pH for absorption (see [Chapter 23](#)). Another example of applying knowledge of age-related pharmacokinetic changes to recommendations for nonprescription medications is that of an older adult who requests assistance in selecting an analgesic. Additional caution is warranted in advising older patients regarding use of NSAIDs because of gastrointestinal changes, cardiovascular issues, and renal function concerns associated with aging (see [Chapter 5](#)).

In addition to the pharmacokinetic changes seen in older adults, the following facts and statistics should be considered in the PPCP:

- Polypharmacy (concurrent use of 5 or more medications) and high risk of adverse drug events
 - More than 1 in 3 older adults take 5 or more prescription medications concurrently.^{63,64}
 - One in 6 older adults are at risk for major drug-drug interactions.⁶³
- Multiple chronic disorders

- Almost 3 in 4 people 65 years of age and older have multiple chronic disorders.⁶⁵
- Alterations in senses⁶⁶
 - One in 6 older adults have impaired vision.
 - One in 4 older adults have impaired hearing.
- Cognition and memory changes
 - Although aging and memory loss are not synonymous, 1 in 10 people 65 years of age and older have Alzheimer disease.⁶⁷
- Misperceptions that deficits or symptoms are part of the aging process instead of a characteristic of a disease or disorder can contribute to underreporting of such problems.⁶⁸
- *Dysphagia* (difficulty swallowing) affects 15% of the older adult population.⁶⁹
- Sensitivity to anticholinergic medications^{70,71}
 - Salivation, lacrimation, urinary output, and gastrointestinal motility are decreased and can cause nutrition problems, blurred vision, urinary retention, and constipation.
 - Cardiovascular system and body temperature regulation are altered.
 - Falls, delirium, and cognitive impairment can occur.
- The role of informal caregivers who provide assistance or participate in making treatment decisions

PPCP Considerations for Geriatric Patients

Specific information to consider during each step of the PPCP for geriatric patients is outlined next.

Collect

- Recognize that the collection step may take additional time in older adults because of the amount and complexity of information needed to make an appropriate assessment.
- Gather more detailed information to perform a comprehensive review of medical conditions and medication history to avoid potential

medication-related problems.

- Consult the pharmacy's prescription medication profile, when available, to identify potential medication-related problems from multiple medications.
 - Ask about known renal and hepatic disease or impairment.
 - Inquire about chronic health problems or disorders that may affect nonprescription medication recommendations or present exclusions for self-care, such as hypertension, diabetes, lung diseases, or Alzheimer disease.
- Observe or ask about sensory impairments (especially in vision and hearing) and memory deficits or signs of cognitive decline.
 - Involve family members or caregivers, when available, if memory impairment or cognitive decline is evident.
 - Include more in-depth questions regarding symptoms that could be unrecognized or falsely attributed to age.
 - Ask about any swallowing difficulties.
 - Inquire about physical limitations that may affect medication use, such as ability to open a medication container or apply topical agents to specific areas.

Assess

- Evaluate for potential duplicate therapy related to polypharmacy.
 - Pharmacists should specifically consider nonprescription medications available with a prescription such as proton pump inhibitors, histamine type 2 receptor antagonists, antihistamines, and analgesics to avoid duplicate therapy.
- Evaluate for potential adverse drug effects.
 - Polypharmacy increases the likelihood of adverse effects⁷²; therefore, current medications should be considered as a potential cause of any new symptom in the older adults until proven otherwise.
 - Several nonprescription medications are listed in the American Geriatrics Society Updated Beers Criteria of Potentially Inappropriate Medication Use in Older Adults.⁷³ This resource contains evidence-based information about safe medication use by older patients, including nonprescription medications

associated with high risk of adverse effects in this population. For example, based on these criteria, diphenhydramine may not be an appropriate recommendation in older adults for the treatment of insomnia and is likely to confer more risk than benefit⁷³ (see [Chapter 46](#)).

- Evaluate whether the normal adult dose is too high.
 - Dosage adjustments may be necessary for nonprescription medications in persons who have renal and/or hepatic impairment, just as with prescription medications. Because nonprescription medications are labeled to allow the patient to safely determine the appropriate drug and dosage without the advice of a health care provider, the Drug Facts label may simply state that patients should avoid taking this medication without medical supervision if they have kidney or liver disease. Labels will not provide the dosage adjustments for specific levels of renal or hepatic dysfunction. The pharmacist's self-care assessment should determine the appropriateness of nonprescription therapy for a patient with impaired renal or hepatic function.

Plan and Implement

- Consider concomitant medical conditions and other medications during product selection.
 - Older adults are more likely to have multiple medical conditions; therefore, product selection based on chronic disease status is warranted in this population. In general, it is best to avoid elixirs and sugar-sweetened liquids in patients with diabetes and to avoid liquids with excessive alcohol content in all older patients.
- Evaluate for nonadherence to medication regimens.
 - Consider the complexity of the patient's current medication regimen. Pharmacists should select products that complement or match timing for dosing with this regimen, when possible.
 - Consider adherence-assistive devices, such as medication reminder boxes, or involve caregivers when appropriate.
- Determine appropriate dosing and administration of medications.
 - Alternative dosage forms or administration methods may be

needed for patients with dysphagia. Determining appropriate dosage forms is a complex process and requires that the pharmacist collaborate with the patient or caregiver and the patient's prescribers. Considerations in making this determination may include, but are not limited to, whether the medication can be crushed, chewed, or thickened, depending on the severity of dysphagia.

- Provide specific patient education and counseling.
 - A patient who is hard of hearing may require the pharmacist to speak slowly in a slightly raised voice, but to avoid yelling, and to consider moving the encounter to an area of reduced noise. Another technique includes, but is not limited to, provision of written instructions if the patient prefers this method of communication.
 - A patient with low vision will need clear, audible instructions regarding product use. Another technique includes, but is not limited, to provision of large-print instructions.
 - Patients with physical challenges such as decreased dexterity associated with arthritis may require selection of a medication without child-resistant closures, and counseling should specifically emphasize the need to keep the product out of the reach of children and pets.
 - Given the high risk of polypharmacy in older adults, it is important to explain all active ingredients in the recommended product, to avoid duplicate therapy.

Follow-up

- As with pediatric patients, certain characteristics of older adults may be relative indications for referral to another health care provider sooner rather than later, to avoid adverse events. This is particularly true for frail older adults whose nutritional status and lower weight may contribute to higher risk for serious consequences if the disorder suddenly worsens or nonprescription therapy is ineffective. Patients who have multiple chronic diseases or limited social support or those with impairments in cognitive function also may require more intensive follow-up strategies.

Pregnant Patients

Drug therapy may be necessary to treat medical conditions or to manage common disorders associated with pregnancy. Many medications cross the placenta to some extent, with associated inherent risk, because a mother who ingests a medication may expose her unborn infant as well. Considerations to ease the mother's discomfort and to limit effects of nonprescription medications on the developing fetus are crucial. Patients should never presume that a nonprescription product is safe to use during pregnancy, and pharmacists should be able to provide well-informed guidance to determine when self-care is appropriate and when referral is needed.

PPCP Considerations for Pregnant Patients

Specific information to consider during select steps of the PPCP for the pregnant patient is outlined next.

Collect

- The pharmacist should ask all female patients of childbearing age who present with common symptoms of early pregnancy, such as nausea and vomiting, if they are pregnant or could be pregnant. Visual observation is not reliable, especially at early stages of pregnancy.
- If pregnancy is confirmed, identify the likely stage of pregnancy. For some medications, packaging includes specific information regarding safety based on the trimester of pregnancy. For example, the Drug Facts label for ibuprofen specifically warns against use in the last 3 months of pregnancy because of risks to the fetus.⁷⁴

Assess

- Evaluate the safety of medication use during pregnancy.
 - The Drug Facts label for specific nonprescription medications may advise the pregnant patient to consult a health care professional before use. The pharmacist should assess the patient's symptoms and determine whether selftreatment is appropriate with a safe product and/or if referral to another health care provider is needed.
 - FDA recently issued a final rule regarding revised pregnancy and

lactation risk categories. Pharmacists should be aware that this new rule applies only to prescription products. The Preface of this book provides a detailed explanation of the pregnancy and lactation data. The new data may include information for some nonprescription medications that also are available as prescription drugs.

- Determine whether the patient's pregnancy status is an exclusion for self-treatment even if a nonprescription product is considered safe for use in pregnancy.
 - For example, calcium carbonate generally is considered the antacid of choice for the pregnant patient; however, heartburn occurring in a patient without formal evaluation and diagnosis by an appropriate health care provider during pregnancy is an exclusion for self-treatment (see [Chapter 13](#)).

Plan and Implement

- Consider nonpharmacologic therapy options in pregnant patients.
 - To minimize medication exposure, the pharmacist may initially recommend nonpharmacologic self-care measures for pregnant patients. For example, in the pregnant patient who presents with allergic rhinitis symptoms, initial nonpharmacologic recommendations may include avoiding triggers, using saline nasal sprays or rinses, or placement of nasal dilating strips to open nasal passages. Even if a safe nonprescription medication for allergic rhinitis is available, pregnant patients may still be referred to another health care provider to confirm that the nonprescription product is safe for use (see [Chapter 11](#)).
- Discourage the use of homeopathic and herbal remedies in pregnancy because safety and effectiveness typically have not been established.
- Evaluate for nonadherence to medication regimens.
 - Because nausea and vomiting are common in early pregnancy, the pharmacist can provide education to minimize their effects on medication adherence. Advising the patient to eat small meals and frequent snacks and crackers may alleviate or minimize nausea and vomiting. Additionally, the patient can be advised to avoid foods, smells, or situations that are likely to cause vomiting.

(see [Chapter 19](#)). When possible, a nonprescription medication schedule should be established to avoid times when nausea and vomiting typically are present or more severe.

Follow-up

- Pharmacists should ensure that the pregnant patient has a clear follow-up plan that includes a specific time frame and appropriate action steps. In general, when the goal of therapy is not met in the intended time frame, a conservative approach includes referral to another health care provider as soon as possible to avoid adverse events.

Lactating Women

Similar to considerations in the pregnant patient, the nursing mother's use of medication while breastfeeding has potential for adverse effects on the infant. This potential for infant exposure is affected by the medication-specific properties and concentrations in the mother's blood, the timing of medication administration, and the medication safety profile in the infant.⁷⁵ The medication's effect on milk supply, as with some decongestants, also should be considered.⁷⁶ The benefit to the mother must again be weighed against the risks to the infant.

PPCP Considerations for Lactating Women

Specific information to consider during select steps of the PPCP for the lactating woman is outlined next.

Collect

- The pharmacist should ask female patients, particularly those who present with an infant or young child, about breastfeeding status. Assumptions or judgments are not appropriate, and professional communication is essential to collect the appropriate information to make the best assessment.

Assess

- Evaluate the safety of medication use during lactation.
 - The Drug Facts label for specific nonprescription medications

may advise the lactating patient to consult a health care professional before use. The pharmacist should assess the patient's symptoms and determine whether selftreatment is appropriate with a safe product and/or if referral to another health care provider is needed.

- FDA recently issued a final rule regarding revised pregnancy and lactation risk categories. Pharmacists should be aware that this new rule applies only to prescription products. The Preface of this book provides a detailed explanation of the pregnancy and lactation data. The new data may include information for some nonprescription medications that also are available by prescription. For example, ranitidine is available as both a prescription and a nonprescription medication, so the detailed pregnancy risk information may be not be consistent for both versions.
 - If pharmacists are unable to ascertain the safety of a medication in breastfeeding, the patient should be referred to her regular health care provider, a lactation consultant, or the child's pediatrician. Pharmacists should encourage the patient to consult with another health care provider before discontinuing breastfeeding to take a nonprescription medication.
 - Consult additional, reliable resources.
- LactMed is a free database, available online and through an application, that is peer reviewed, recommended by AAP, and maintained by the National Library of Medicine.⁷⁷ The database contains information on maternal and infant drug levels, effects on lactation and in breastfed infants, and alternative drugs to consider.^{75,78}

Plan and Implement

- Consider nonpharmacologic therapy options.⁷⁹
- Choose medications with the shortest half-life.⁷⁹

Discourage the use of homeopathic and herbal remedies during lactation, because safety and effectiveness typically have not been established.⁷⁵

Follow-up

Pharmacists should ensure that recommendations made to women who are

lactating include a clear follow-up plan with a specific time frame and appropriate action step. When therapeutic goals are not met in the intended timeframe, quick referral to another health care provider is advisable to avoid adverse events.

Case 2-1

A 35-year-old woman who is a regular patient of yours was just stung by a bee on her way to your pharmacy to pick up a prescription. She wants to know what she should do to stop the burning.	
Information to Obtain from the Patient	What the Patient Told You
Quickly and accurately assess the patient:	
Ask about the current problem (SCHOLAR).	
<u>Symptoms</u>	
What are the main and associated symptoms?	"Pain from a bee sting on my right hand."
<u>Characteristics</u>	
What is the situation like? Is it changing?	"Burning, itching, and redness." [Pharmacist notices mild, localized erythema with no signs or symptoms of systemic anaphylaxis.]
<u>History</u>	
What has been done so far? Has this ever happened before, and if so, what was done then? What was successful, and what wasn't?	"Nothing, because it just happened." "This is the first bee sting I've ever experienced."
<u>Onset</u>	
When did it start?	"Five minutes ago as I was walking from my car to the

	pharmacy.”
<u>L</u> ocation	
Where is the problem?	“The palm of my right hand.”
<u>A</u> ggravating factors	
What makes it worse?	“When I touch the bee sting area.”
<u>R</u> emitting factors	
What makes it better? Ask about other <u>M</u>edications, <u>A</u>llergies, and <u>C</u>onditions (MAC): Within reason, get as much detail as possible to assist in the decision-making process.	“I haven’t tried anything yet.” • “I take levothyroxine 50 mcg every day.” • “I’m not allergic to any medications.” • “This is the first time I’ve ever had a bee sting.”
The “E.S.T.” pieces of QuEST: Establish, Select, and Talk	Your Assessment, Recommendation, and Counseling
<u>E</u>stablish that the patient is an appropriate self-care candidate: • Any severe symptoms? • Any symptoms that persist or return repeatedly? • Is the patient self-treating to avoid medical care? <u>S</u>uggest appropriate self-care strategies.	• Symptoms are mild and localized to the right hand. Because this was her first bee sting, the risk of hypersensitivity is low. • She is not exhibiting any signs of an anaphylactic reaction, such as hives, swelling, dizziness, weakness, or difficulty breathing. • <i>Nondrug</i>: Remove the stinger by scraping with a credit card immediately; then apply an ice pack or cold compress. • <i>Medication</i>: Apply local anesthetic, such as benzocaine 20% aerosol spray, to affected area 3–4 times daily for up to 7 days to reduce itching and burning.
<u>T</u> alk with the patient about	Key Counseling Points:

• Medication action, administration, and adverse effects • What to expect from the treatment • Appropriate follow-up	• “I think you can do a few things to help this situation. Benzocaine is a topical anesthetic that will help relieve itching and irritation associated with the bee sting. Spray the affected area 3–4 times daily for up to 7 days. If the site becomes more irritated or redness increases, stop using the spray.” • “The benzocaine should provide immediate relief. The symptoms should resolve over time and should not last longer than 1 week.” • “If you experience any hives, excessive swelling, dizziness, vomiting, or difficulty breathing, seek medical attention immediately. If you feel your condition is getting worse or your symptoms have not resolved by 1 week, seek medical attention.” • “Keep the area clean by washing regularly with soap and water; do this before each application of benzocaine.”

Case 2–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient’s symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient complains of difficulty sleeping. He describes difficulty falling asleep about 2–3 nights a week and has early awakening with inability to fall back to sleep 5–7 days a week. “I just don’t sleep very well anymore, and I wonder if there’s something I can take that will help.” Symptoms started approximately 1 month ago.
b. Description of any factors	He sometimes, but not always, has “better sleep” if he sleeps

Relevant Evaluation Criteria	Scenario/Model Outcome
that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	upright in a recliner chair instead of the bed.
c. Description of the patient's efforts to relieve the symptoms	He tried melatonin 3 mg daily before bedtime last week for 3–4 nights with no relief.
d. Patient's identity	James Markum
e. Patient's age, gender, height, and weight	81 years, male, 5 ft 9 in., 170 lb
f. Patient's occupation	Retired railroad worker
g. Patient's dietary habits	Normal balanced diet. He drinks 3 cups of caffeinated coffee daily; no alcohol.
h. Patient's sleep habits	Averages 5–6 hours per night. Naps 1–2 times per day in morning and/or afternoon.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	<i>Gastroesophageal reflux disease</i> : omeprazole 20 mg daily; <i>hypertension</i> : hydrochlorothiazide 25 mg daily, lisinopril 20 mg daily; <i>depression</i> : sertraline 100 mg daily; <i>Alzheimer dementia</i> : donepezil 5 mg daily
j. Allergies	NKA
k. History of other adverse reactions to medications	None
l. Other (describe) _____	None
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Insomnia, possibly secondary to current medical conditions
3. Identify exclusions for	Age ≥65 years, chronic insomnia (>3 weeks), sleep disturbances

Relevant Evaluation Criteria	Scenario/Model Outcome
self-treatment.	possibly secondary to medical disorders
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer the patient to his regular health care provider. (2) Recommend self-care with lifestyle modifications for good sleep hygiene and diphenhydramine. (3) Recommend self-care until the patient can see his primary care provider.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Patient should consult his primary care provider.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"I recommend you see your primary care provider for treatment of your sleep problems."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"This is the best option for you since you have had the sleep problems for several weeks and your situation may be related to your current medical conditions. Also, the nonprescription medications typically used to treat sleep problems are not the best option for you. You may require prescription medications or adjustments of your current medications by your primary care provider."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey	Criterion does not apply in this case.

Relevant Evaluation Criteria	Scenario/Model Outcome
accurate information to the patient or caregiver.	
Solicit follow-up questions from the patient or caregiver.	"Are there any drugs I can take to help until I get an appointment with my physician?"
Answer the patient's or caregiver's questions.	"No—you tried the melatonin and it didn't work. There are no other nonprescription medications that are safe and effective for your sleep problems. I recommend contacting your primary care provider for an appointment. If you are unable to see your provider immediately, you can try to improve your sleep by avoiding or reducing caffeine, avoiding daytime naps, and participating in something relaxing before bedtime, such as reading."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Mr. Markum in 1-2 days to ensure that he has sought medical care for insomnia.

Key: NKA = No known allergies; PCP = primary care provider.

Case 2–3

The mother of a 3-month-old boy calls the pharmacy requesting advice for her son's gastrointestinal illness: He has had several watery stools since yesterday.

Information to Obtain from the Patient	What the Parent Told You
<u>Quickly</u> and accurately assess the patient:	

Ask about the current problem (SCHOLAR).	
<u>S</u> ymptoms	
What are the main and associated symptoms?	"My son has had watery diarrhea since yesterday."
<u>C</u> haracteristics	"The stool is very thin and has no consistency at all. He's breastfed, and he has stopped eating the last few hours. He seems more tired and has not had a wet diaper for several hours."
What is the situation like? Is it changing?	
<u>H</u> istory	
What has been done so far? Has this ever happened before, and if so, what was done then? What was successful; what wasn't?	"I haven't given him anything to stop the diarrhea."
<u>O</u> nset	
When did it start?	"About 24 hours ago."
<u>L</u> ocation	
Where is the problem?	"Just diarrhea. No vomiting."
Aggravating factors	
What makes it worse?	"Nothing."
<u>R</u> emitting factors	
What makes it better?	"Nothing."
Ask about other <u>M</u> edications, <u>A</u> llergies, and <u>C</u> onditions (MAC): Within reason, get as much detail as possible to assist in the decision-making process.	• "My son takes D-Vi-Sol Vitamin D drops daily." • "He's not allergic to anything that I know of." • "He is otherwise very healthy. This is the first time he has been sick."

The “E.S.T.” pieces of QuEST: Establish, Select, and Talk	Your Assessment, Recommendation, and Counseling
Establish that the patient is an appropriate self-care candidate. - Any severe symptoms? - Any symptoms that persist or return repeatedly? - Is the patient self-treating to avoid medical care? Suggest appropriate self-care strategies.	The child’s symptoms are considered severe because he is younger than 6 months and has diarrhea with signs of moderate to severe dehydration. He is not a candidate for a self-care management approach. “There aren’t appropriate nonprescription treatments to help your son, because he is so young. You should call your pediatrician immediately. Your son may need fluids that could be given only in an emergency department.”
Talk with the patient about - Medication action, administration, and adverse effects - What to expect from the treatment - Appropriate follow-up	Key Counseling Points: “Because your child is so young and has diarrhea, you should contact your son’s pediatrician immediately to ensure that he gets the fluids and help he needs to prevent becoming dehydrated.”

Case 2–4

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient’s symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient complains of a burning sensation in her stomach and throat that often is accompanied by feelings of fullness and “acid in my throat.” The

Relevant Evaluation Criteria	Scenario/Model Outcome
	burning occurs after a heavy meal no more than once weekly. Symptoms began about 1 month ago and last 2–4 hours after a meal.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Symptoms occur after eating lunch out with coworkers or after potlucks at work and last for 2–4 hours after the meal.
c. Description of the patient's efforts to relieve the symptoms	Eating a few peppermint candies did not help with symptoms. She tried Tums (calcium carbonate 500 mg) once without full symptomatic relief.
d. Patient's identity	Maria Flores
e. Patient's age, gender, height, and weight	43 years, female, 5 ft 4 in., 175 lb
f. Patient's occupation	Office assistant
g. Patient's dietary habits	Normal balanced diet. She drinks 4 or 5 cups of caffeinated coffee daily; 3 or 4 alcoholic beverages once per week.
h. Patient's sleep habits	Averages 7–9 hours per night.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	No concurrent medical conditions; multivitamin daily
j. Allergies	NKA
k. History of other adverse reactions to medications	None
l. Other (describe) _____	Weight gain of 10 lb in the past 3 months
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Infrequent postprandial burning sensation is consistent with uncomplicated heartburn. Patient denies pregnancy.
3. Identify exclusions for self-treatment.	None

Relevant Evaluation Criteria	Scenario/Model Outcome
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required and share this information with the patient or caregiver.	Options include (1) Refer the patient to her regular health care provider. (2) Recommend self-care with lifestyle modifications and nonprescription acid-reducing medication. (3) Recommend self-care until the patient can see her primary care provider.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	A nonprescription acid-reducing medication along with lifestyle modifications should be effective.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"There are a number of things you can do on your own to decrease your symptoms. In addition, I recommend that you use the acid-reducer famotidine 20 mg for additional relief."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"This medication is a reasonable first option for treating your symptoms before consulting your primary care provider. Because the heartburn is predictable with large meals, primarily after lunch, using the famotidine on an as-needed basis should be sufficient."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
a. Appropriate dose and frequency of administration	"Swallow one tablet 10–60 minutes before eating food or drinking beverages that typically cause heartburn."
b. Maximum number of days the	"You can use this for up to 14 days in a row, if

Relevant Evaluation Criteria	Scenario/Model Outcome
therapy should be employed	needed. If you think you need it beyond that time, call your primary care provider for an appointment. From what you said, I can't imagine you'll need this medication more than once a week, if that."
c. Product administration procedures	"Be sure to take this medication with a full glass of water."
d. Expected time to onset of relief	"You should feel better a few hours after you take this medication. Often the relief happens sooner."
e. Degree of relief that can be reasonably expected	"You should expect at least some relief; often patients get complete relief with a single dose."
f. Most common adverse effects	"Some of the more common adverse effects are headache, diarrhea, dizziness, and constipation, but these don't happen too often and are rarely serious."
g. Adverse effects that warrant medical intervention should they occur	"If you experience any unusual bleeding or bruising, be sure to call your primary care provider and stop using this medicine."
h. Patient options in the event that condition worsens or persists	"If this situation worsens, please consult your primary care provider."
i. Product storage requirements	"Store this medicine in a cool dry place out of the reach of children."
j. Specific nondrug measures	"Other things that can help you include eating smaller, more frequent meals and avoiding or eating less of foods and drinks that cause your symptoms."
Solicit follow-up questions from the patient or caregiver.	"May I take the medication after I start the meal if I have forgotten to take it beforehand?"
Answer the patient's or caregiver's questions.	"Yes, but the medication may not be as effective in preventing heartburn symptoms."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	To evaluate efficacy of the treatment, advise Mrs. Flores to call the pharmacy to report her response after using the medication as needed for heartburn prevention.

Key: NKA = No known allergies.

Key Points for PPCP in Self-Care

- Pharmacists play an active role in assisting patients with selfcare by using the five key PPCP components: collect, assess, plan, implement, and follow-up: monitor and evaluate.
- The PPCP is the same process for self-care encounters as it is with any other pharmacist-provided patient care service and in any practice setting. The process is adaptable, depending on the breadth and depth of care needed.
- Collecting essential information for the specific presenting medical condition will lead to an appropriate assessment and may identify unique considerations in self-care, such as exclusions for self-treatment.
- The plan should include the self-care recommendation, including nonpharmacologic therapies, and the goal of therapy to identify anticipated outcomes of the recommendation and the time frame in which the outcome is expected.
- Follow-up in self-care encounters should include specific guidance on what action to take for efficacy or safety considerations. Such guidance may include resolution of the self-care disorder with no further action needed, a return to the pharmacist for additional assessment, selection of an alternative nonprescription medication, or medical referral.
- The PPCP in self-care has patient-centered care at its core, with continual collaboration, communication, and documentation of care with other health care providers.

- Efficiency in the PPCP is imperative in a community pharmacy. Tools such as QuEST/SCHOLAR-MAC and the algorithms for specific disorders in this book serve as resources to streamline the process and assist in quick and accurate application of the process in this practice setting.
- Special populations, which include pediatric patients, older adults (geriatric patients), pregnant women, and lactating patients, are at increased risk for serious adverse events if not appropriately assessed.
- Using the PPCP in self-care encounters for special populations may take additional time because of the amount and complexity of information needed for an appropriate assessment.

Chapter 3: Exploring Cultural Aspects of Self-Care

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Cultural background, identity, and characteristics are well recognized to influence patients' specific health care beliefs and behaviors.^{1,2} This chapter explores cultural aspects of self-care to guide health care providers in diverse practice settings, and often of various cultural and ethnic backgrounds themselves, to better understand patient health decisions and to develop individualized approaches to patient education. Formulation of a successful and appropriate self-care plan for a given health issue is best achieved by incorporating the patient's health beliefs and behaviors as a key component of the plan. If cultural and diversity issues are not identified and considered early in the clinical encounter, the health care provider may find challenges with assessing medical problems and educating patients effectively, and patients may have difficulty accepting and implementing self-care recommendations.¹⁻³

In clinical pharmacy practice, recognition of cultural context in patients' self-care decisions related to overall health requires familiarity with basic concepts in this aspect of service. Accordingly, this chapter begins by defining important cultural and diversity terms and then reviews theoretical frameworks for cross-cultural care. Next, demographic shifts in the composition of the U.S. population are outlined to illustrate the relevance of serving diverse populations, along with socioeconomic considerations, in the delivery of self-care health services. Examples of cultural behaviors found in various populations across the United States also are presented, with a focus on differences in cultural approaches to seeking care, particularly self-care. In this context, a valuable resource developed by the Joint Commission of Pharmacy Practitioners is the Pharmacists' Patient Care Process, which can be applied to optimize clinical interactions with marginalized populations and to assist health care providers in developing more inclusive and culturally sensitive treatment plans. This sequential process serves as the framework for the clinical cases presented throughout the book⁴

Definitions

Culture can be understood as an “integrated pattern of human behavior that includes thoughts, communications, languages, practices, beliefs, values, customs, courtesies, rituals, manners of interacting, roles, relationships and expected behaviors of a racial, ethnic, religious, or social group; the ability to transmit the above to succeeding generations; and is dynamic in nature.”⁵ Culture can influence all aspects of human behavior. Of particular importance is the role of culture in health-seeking and health maintenance behaviors and how these health beliefs and practices are passed from generation to generation.

A more succinct definition of culture is the sum total of socially inherited characteristics of a human group. This set of characteristics derives from assumptions learned from family and society about the nature of the physical, social, and spiritual world, as well as the goals of life and acceptable ways by which they can be achieved.² Culture—as a learned set of values, beliefs, and meanings—guides patient decisions, attitudes, and actions.

In this chapter, the term *Western medicine* (also viewed as *allopathic* or *conventional medicine*) refers to therapies based on science and regulated by the U.S. Food and Drug Administration (FDA), including prescription and nonprescription products. The term *complementary and alternative medicine* (CAM) encompasses Eastern and traditional medicine approaches. Of note, *complementary* often refers to therapy used in concert with Western medicine, and *alternative* often designates therapy used in the place of conventional medicine.⁶ Examples are magnet therapy, acupuncture, dietary supplements, mind–body techniques, homeopathy, and massage therapy. The concept of CAM is introduced in this chapter to promote awareness among health care providers of the potential use of such modalities in various patient populations. (See [Chapters 50](#) and [51](#) for an in-depth discussion of CAM.) *Integrative medicine* recognizes evidence-based approaches using a balance of conventional therapies with CAM. (See [Chapter 52](#) for a discussion of complementary and integrative medicine [CIM].) These concepts of Western medicine, CAM, and CIM can help to shape how health care providers understand self-care behaviors across a range of patient populations.⁶

Literature suggests that health care providers who can navigate among cultures and languages can integrate awareness, knowledge, skills, and commitment that lead to development of cultural respect, sensitivity, humility, and competence.^{3,7,8} By conveying *cultural respect*, providers optimize the

value of the clinical interaction by being “respectful of and responsive to the health beliefs, practices and cultural and linguistic needs of diverse patients.”⁷ Providers who are *culturally sensitive* consistently model attitudes and behaviors that reflect patients’ views of respect and acceptance of diversity.⁸ These providers may partner with patients to include their needs, values, and preferences in treatment plans.⁸ Patients are empowered to be in control of their health and health care decisions.⁸ *Cultural humility* refers to the “ability to maintain an interpersonal stance that is other-oriented (or open to the other) in relation to aspects of cultural identity that are most important to the [person].”⁹

Although several definitions exist, *cultural competence* is perhaps best described as the ability to provide “effective, equitable, understandable, and respectful quality care and services” that honor and respond to a diversity of cultural health attitudes, beliefs, practices, and language preferences while accounting for health literacy and other interpersonal communication styles and behaviors.^{3,5} When providers are able to communicate information appropriate to populations with unique language, literacy, and abilities in an effective and easy to understand way, they are employing *linguistic competency* skills.¹⁰ To support culturally and linguistically competent practices, organizational leadership should be able to plan, implement, and evaluate supportive policies, programs, and interventions to ensure delivery of high-quality health care services.⁵

Rationale for Exploring Cultural Aspects of Self-Care

Demographic Changes in the U.S. Population

The U.S. government classifies people into five races: (1) African American or black, (2) American Indian or Alaska Native, (3) Asian, (4) Native Hawaiian or Other Pacific Islanders, and (5) white ([Table 3–1](#)).¹¹ Although agreement on a uniform way of referring to race (beyond the human race!) is lacking, in this chapter, these five categories—alone or in combination—are used. In addition to race, people may identify themselves in terms of ethnicity, such as “Hispanic or Latino” or “not Hispanic or Latino”; accordingly race and Hispanic origin are considered two separate categories. For example, a person may self-classify as

non-Hispanic white, Hispanic white, non-Hispanic black, or Hispanic black. Historically the term *minority* refers to populations of people who do not self-identify as non-Hispanic white. To collect data, government agencies rely on respondents to the U.S. Census and other surveys and questionnaires to self-report or self-identify their race and ethnicity, with the opportunity to choose two or more races. The issue of defining race and ethnic background is increasingly complex. Research studies and epidemiology reports also compare persons from diverse races and ethnicities as a way to elucidate the basis for health disparities and to identify opportunities for improving care.

TABLE 3–1 U.S. Census Classification of Race and Ethnicity Based on Origin

Race^a (self-identified)	Population Origins
African American or Black	Any of the black racial groups stemming from Africa
American Indian or Alaska Native	Indigenous peoples of North and South America (including Central America) who also affiliate with a tribe or are attached to a community
Asian	Any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam
Native Hawaiian or Other Pacific Islander	Peoples with origins in Hawaii, Guam, Samoa, or other Pacific Islands
White	Original populations stemming from Europe, the Middle East, or North Africa
Ethnicity (self-identified)	Population Origins
Hispanic or Latino	Cuban, Mexican, Puerto Rican, or South or Central American or other Spanish culture or origin regardless of race
Non-Hispanic or non-Latino	Non-Hispanic/non-Latino culture or origin

^a In the U.S. Census, race constitutes a “social definition” that is based on “racial and national origin or sociocultural groups.” Because race is self-identified in the Census, it does not require a link to a “biologic, anthropologic, or genetic” origin. Also, federal standards mandate that race and Hispanic origin (ethnicity) are separate and distinct concepts.

Source: [Reference 11](#).

The heterogeneity of the race and ethnicity classification options as defined by the U.S. government is important to recognize. For example, the groups included under Asian (e.g., Southeast Asia, East Asia, and South Asia) and Pacific Islanders exhibit great variability. This distinction also is true for the Hispanic classification, which includes four diverse groups: Mexican Americans, Puerto Ricans, Cubans, and others (e.g., Central Americans, South Americans, Spaniards). While classified as white in the 2010 U.S. Census data, populations whose ancestors come from countries such as Lebanon, Egypt, Syria, Palestine, and Morocco are a growing group self-identifying as Arab Americans, at an estimated 0.5% of U.S. residents.¹²

The reported number of minorities has resulted in a shift in the composition of the U.S. population ([Table 3–2](#)).^{13–15} In perspective, one of every three U.S. residents identifies as a minority, that is, a person who is from a non-white race. By 2044, more than one half of the U.S. population is expected to identify with a racial and ethnic group other than white.¹³ Currently, persons who identify as Hispanic constitute the largest minority population, followed by blacks and Asians. The most rapidly growing populations consist of persons who identify as being of (1) two or more races, (2) Asian, or (3) Hispanic background.

TABLE 3–2 Population Characteristics in the United States (2000, 2010–2018)

Characteristic	Total Population^a 2000	Total Population^a 2018	Total Population Projected 2050
Total population ^b	281.4 million	327.2 million	439.01 million

Characteristic	Total Population^a 2000	Total Population^a 2018	Total Population Projected 2050
		% of Total Population	
Race (self-identified)			
African American or Black	12.3	13.4	13.0
Asian	3.6	5.8	7.8
American Indian and Alaska Native	0.9	1.3	1.2
Native Hawaiian and Other Pacific Islanders	0.1	0.2	0.3
White (non-Hispanic or Latino)	69.1	60.7	46.3
Two or more races	2.4	2.7	3.7
Ethnicity: Hispanic or Latino (any race)	12.5	18.1	30.2
Age 65 years and older	12.4	15.6	19.1
Education, less than 12th grade ^c	19.6	12.7	n/a
Language other than English spoken at home (up to and including the age of 5 years)	17.9	21.3(2013-2017)	n/a

^a Total is greater than 100% because of some cross-classification in Census data.

^b Based on race alone or in combination with one or more other races.

^c Less than 9th grade; 9th–12th grade, no diploma (in persons 25 years of age and older).

Key: n/a = Not applicable.

Source: References 14 and 15. Additional source: <https://www.census.gov/content/dam/Census/library/working-papers/2009/demo/us-pop-proj-2000-2050/analytical-document09.pdf>. Accessed July 19, 2019.

Other changes in the landscape of health care delivery include the emergence or predominance of other groups of minorities or underserved populations. Trends in migration patterns have created unevenly distributed racial and ethnic subpopulations across the United States.¹⁵

With the increase in the number of adults 65 years of age and older, this age group now makes up 14.9% of the population ([Table 3–2](#)).¹⁵ Approximately one half of older adults 75–85 years of age use nonprescription medications.¹⁶ Populations composed of persons identifying as American Indian and Alaska Native have demonstrated the highest rates of self-reported CAM use (>50%), followed by white (43.1%) and Asian (39.9%).¹⁷ These changes have created diversity in ethnic consumer markets that may be more pronounced in certain regions of the United States. In a 2012 survey conducted by the U.S. Department of Health and Human Services, the use of complementary health approaches including, but not limited to, dietary supplements, deep breathing exercises, and yoga was reported by 37.9% of non-Hispanic whites, 37.3% of non-Hispanic other races, 22% of Hispanics, and 19.3% of non-Hispanic blacks.¹⁸

Beyond changes in race, ethnicity, and age characteristics, the U.S. population is becoming more diverse in terms of gender identity, gender expression, sexual orientation, socioeconomic status, physical abilities, veteran status, and religious affiliation. An estimated 4.5% of Americans in 2017 identified as lesbian, gay, bisexual, and/or transgender (LGBT).¹⁹ In 2014, 27.2% of Americans reported having a disability, with 17.6% of the disabilities classified as severe.²⁰ According to the U.S. Census, in 2017, 12.3% of Americans, or an estimated 1 in 8 persons, reported living below the poverty level, and more than 18.9 million identified as veterans.¹⁵

The religious landscape in the United States also is changing. Between 2007 and 2014, U.S. population groups who identify themselves as Christian have decreased from 78.4% to 70.6%, and an increasing percentage of people in this country do not affiliate with any religion (22.8% in 2014, versus 16.1% in 2007). Nearly 6% of the U.S. population in 2014 is aligned with non-Christian faiths compared with 5% in 2007.²¹ These national demographic changes across race classifications, socioeconomic status, religion, and other traits have increased the importance of health care provider education and training in diversity, cultural sensitivity, and provision of culturally appropriate services. To explore demographic, social, and economic characteristics in any given community in the United States, providers can type the relevant address or zip code for the

population they serve using the U.S. Census resource American Factfinder (<http://factfinder.census.gov>).

Health Disparities

Although the health status of some racial and ethnic groups has improved, health disparities persist among different populations.^{22,23} In many cases, health disparities cannot be explained solely on the basis of information about characteristics of racial and ethnic groups. *Health disparities* or inequities occur when differences or gaps exist in health determinants (e.g., clean air, safe communities), health access (e.g., insurance, transportation), and/or health outcomes (e.g., heart disease, diabetes) among particular populations or groups (e.g., based on race classification, socioeconomic status, disability, or other cultural identities) that have experienced marginalization.^{24,25} These differences often are connected to socioeconomic, political, and/or environmental challenges.

Individuals from some minority groups do not equally experience long life spans, good health, and access to appropriate health care services. For example, low rates of cancer screening and treatment among minority groups are attributed to cultural and linguistic barriers, as well as limited access to health services.²⁵ In the period 2013–2015, medically diagnosed diabetes prevalence rates were higher among American Indian/Alaskan Natives, non-Hispanic blacks and Hispanics, and persons with less than a high school education than among non-Hispanic whites and persons with higher education levels.²⁶ Other health disparities among different races and ethnicities continue to be identified ([Table 3–3](#)), many of which have a link to self-care.

TABLE 3–3 Examples of Health Disparities Among Racial and Ethnic Groups in the United States

Condition	Rate	Potential Self-Care Link
Obesity prevalence (2015–2016)	Hispanics (47%)	Approaches to health and wellness, request for diet or weight loss supplements
	Non-Hispanic blacks (46.8%)	
	Non-Hispanic	

Condition	Rate	Potential Self-Care Link
	whites (37.9%)	
	Non-Hispanic Asians (12.7%)	
HIV incidence, new diagnoses (2017)	Gay and bisexual men (66%)	Acceptance of “safer sex” prevention and practices
	Black/African American (43%)	
	Hispanic/Latino (26%)	
	White (26%)	
	Asian (2%)	
	Multiple races (2%)	
	American Indian/ Alaska Native (1%)	
	Native Hawaiian/ Other Pacific Islander (<1%)	
Heart disease age-adjusted rate of death/100,000, males (2016)	Non-Hispanic black (265.0)	Willingness to use low-dose aspirin for secondary prevention, use of home blood pressure monitoring
	Non-Hispanic white (213.9)	
	American Indian/ Alaska Native (147.7)	
	Hispanic (144.6)	
	Asian/Pacific Islander (106.6)	

Key: HIV, human immunodeficiency virus (infection).

Sources: Centers for Disease Control and Prevention. Adult obesity facts. Available at: <https://www.cdc.gov/obesity/data/adult.html>. Accessed February 2, 2019.

Centers for Disease Control and Prevention. Basic Statistics. Available at: <https://www.cdc.gov/hiv/basics/statistics.html>. Accessed February 2, 2019.

Centers for Disease Control and Prevention. Death rates for diseases of heart, by sex, race, Hispanic origin and age: United States selected years 1950–2016. Available at: <https://www.cdc.gov/nchs/data/hus/2017/022.pdf>. Accessed February 2, 2019.

Among the complex factors explaining health disparities across population groups are race classification, socioeconomic status, literacy, health practices, and social determinants of health that may be harmful or helpful. Some of the negative determinants that contribute to health disparities include psychosocial stressors, lack of resources, environmental exposures, discrimination, unfavorable sociopolitical policies, and limits on access to health care.²² These factors will influence future patterns of disease, disability, and health care utilization unless they are addressed with appropriate remediation. For example, in 2014–2016, when compared with the non-Hispanic white population, blacks, Hispanics, Asians, and American Indians/Alaska Natives experienced worse access to care.²³ In 2016, 20.9% of people with a disability lived below the poverty line, compared with 13.1% of people without disabilities.²⁷

In an effort to create a healthier society and develop strategies to decrease the gap in health care, the U.S. government has guided public health policy over 3 decades through the Healthy People initiative.²⁴ By setting health care priorities and measurable objectives, Healthy People programs create a foundation for the health care agenda for each decade (with the most recent transition from Healthy People 2020 to Healthy People 2030). The newest Healthy People 2030 overarching goals are as follows:

- 1) attain healthy, thriving lives and well-being, free of preventable disease, disability, injury and premature death,*
- 2) eliminate health disparities, achieve health equity, and attain health literacy to improve the health and well-being*

of all, 3) create social, physical, and economic environments that promote attaining full potential for health and well-being for all, 4) promote healthy development, healthy behaviors and well-being across all life stages, 5) engage leadership, key constituents, and the public across multiple sectors to take action and design policies that improve the health and well-being of all.^{20,28}

Several specific Healthy People 2020 objectives reported for the past decade are linked to self-care strategies such as selfmonitoring blood glucose in diabetes, taking measures to prevent sunburn, and making attempts to quit smoking.²⁴ With such objectives, the Healthy People initiative serves as a road map to better health and can be used by different populations, communities, professional organizations, and other groups to improve overall health.

Culturally Appropriate Health Care and Workforce Diversity

One of the factors identified by government agencies and health care groups contributing to health disparities is the lack of awareness of cultural issues and health disparities among health care providers that may be attributed to inadequate formal education on cultural issues in academic health-related training programs.²⁹ To ensure effective delivery of culturally and linguistically appropriate health care in cross-cultural and diverse settings, an understanding of basic diversity and cultural issues related to health and illness, health disparities among different groups, and communication strategies for working with culturally diverse patients is essential.³⁰

Although cultural competence and diversity education are required as part of accreditation in health professional training, lack of workforce diversity still exists in the health care arena.³⁰ This reality highlights the need for providers of all backgrounds and identities to recognize the influences of culture in health care and for health sciences curricula to incorporate content on cultural humility, respect, and competence. The current racial and ethnic group composition of health care providers in the United States does not reflect the composition of the general population. For example, only 4.4% and 7.3% of the first professional-degree pharmacy graduates in 2016 were Hispanic and black or African American, respectively. In the period 2015–2016, 19% of pharmacy

school applications were from underrepresented minority groups.³¹ The pharmacy student and graduate cohorts do not proportionately represent the U.S. population that they will serve. Across health professions, diversification of the health care workforce is needed, both for providing access to health care education and for improving representation of the multitude of populations found in the United States.³⁰

In 2000, the Office of Minority Health, of the U.S. Department of Health and Human Services, developed the National Standards for Culturally and Linguistically Appropriate Services (CLAS) in Health and Health Care.³² These standards, updated in 2013, are based on an in-depth review of the literature, regulations, laws, and standards currently used by federal and state agencies. The CLAS standards provide guidance for individuals and organizations to implement services that are culturally and linguistically appropriate to “advance health equity, improve quality, and eliminate health care disparities.” The 15 standards are divided into four main sections that address (1) the principal standard (used in this chapter’s definition for cultural competence); (2) governance, leadership, and workforce; (3) communication and language assistance; and (4) engagement, continuous improvement, and accountability.

Concepts of Working Across Cultures

Stereotyping and Generalization

Unique persons with slightly different characteristics or beliefs may belong to the same cultural group. However, individual differences within cultural groups also must be considered. In this context, the rational error of *stereotyping* is associated with serious risks to the quality of health care delivered. By contrast, the process of developing a *generalization* may provide a starting point for considering cultural influences in patient self-care. Providers should be cautious, however. When overapplied, generalizations can still lead to potentially misleading or otherwise adverse consequences.

Stereotyping may be viewed as an assumption (often negative) about behaviors or characteristics exhibited by a group of people.¹ Generalization, or predicting that a member of a specific group will often behave in the same manner for that group, may be based on documented or self-described behaviors or characteristics found in subpopulations or cultures. As examples,

stereotyping would be that all minority groups use CAM, and generalization would be that a high rate of CAM use is common in many cultural and ethnic minorities, so it is important to inquire about CAM use.

During each clinical encounter, the patient should be treated as an individual with unique beliefs and values. The provider should avoid stereotyping and be self-aware of making generalizations about groups of people. Rather than relying on such assumptions, asking patients open-ended questions will most effectively assess potential mitigating cultural factors including food selection, sexual practices, caregiver responsibilities, living situation, activity level, and alcohol, tobacco, or illicit substance use. A knowledge base that includes a general idea of behaviors and characteristics of groups of people can help expand awareness of potential health beliefs and behaviors. Familiarity with “typical” health-related practices and lifestyles that may influence disease state prevalence or acceptance of self-care treatment for commonly encountered groups can positively shape patient encounters, treatment plans, and recommendations. Knowing or inquiring about cultural communication preferences, such as salutation, preferred language, eye contact, spatial distance, and physical touch, also is important to facilitating interactions with persons of various populations.

Acculturation

Variations in behaviors among members of a group become more important when people belonging to a specific cultural group migrate to and live in places that have a different, but dominant, culture. *Acculturation* is a process whereby members of a specific cultural group adopt the beliefs and behaviors of a dominant group, but they may still value and practice their own traditional beliefs and behaviors when in the presence of their original group members.² Acculturation can occur when individuals and/or families find themselves adjusting to a different culture, community, or geographical region, or to an entirely new country.

One model identifies four levels of acculturation based on the degree to which people who resettle retain a home culture and/or adapt to a new host culture.³³ People who are able to function well in both their home culture and their host culture can *integrate* cultures; such persons often are able to navigate back and forth between cultures. Persons who adopt the new host culture but let go of their original home culture are said to *assimilate*; they

function well in the host culture but may retain little knowledge of or familiarity with the cultural heritage or language of their forebears. Some people may live between cultures and feel *separated* because they do not fit into either the new host culture or the home culture. Other persons who have moved to a new country, region, or even neighborhood, but who hold onto their home culture and/or language and never fully adopt the new host culture or language, may feel *marginalized*. For example, if a health care provider has been raised in an urban environment on the West Coast (home) and moves to rural Appalachia (host), it may take years for the person to gain a sense of fitting in or even an understanding of community norms. During the acculturation process, people who are influenced by the host culture may behave differently from the norms of their home culture.

Although acculturation is often directed at a new group adopting habits and language patterns of the dominant host group, the outcomes of acculturation can be reciprocal. The dominant host group may in turn adopt patterns typical of the new group. The adoption of ethnic or regional idiomatic expression and the enjoyment of different foods, music, festivities, and dress that represents a particular group are examples of reciprocal acculturation practices. Another example is that of a health care provider who self-identifies as a black male without a religious affiliation (home) relocates to work in a community pharmacy serving a predominantly Islamic community (host). To connect with patients, this provider makes an effort to participate in activities sponsored by the mosque and begins to adopt dietary and behavioral nuances characteristic of the host community culture.

When individuals lose or modify their cultural identity to acquire a new identity that differs from their original cultural group (*assimilation*), the new behaviors and adaptations may cause internal conflicts among members of the original group. For example, conflicts can arise when younger members of a cultural group (e.g., second- or third-generation immigrants) do not follow traditions of the older generation and start to exhibit behaviors and beliefs more consistent with the host culture. In some instances, the children of immigrants may not speak their parents' native language. Culture and acculturation can influence personal beliefs and attitudes toward health, illness, and treatment, as well as decisions regarding health and self-care issues. When providers do not understand a patient's culture, beliefs, and behaviors, the effective delivery of patient-centered care and, consequently, the achievement of optimal health outcomes may be impeded. Incongruent

beliefs and expectations between the provider and the patient may lead to misunderstandings, confusion, and, ultimately, refusal of treatment and undesirable therapeutic outcomes.

Models of Cultural Competence

Developing cultural competence is a continuous and dynamic process that should be consciously undertaken to ensure that health care is delivered in an effective manner among diverse populations of patients and providers. Three common models describe cultural competence as a process versus an achievement and can be used by providers who support patients as they seek self-care therapy options (Table 3–4).^{34–36}

TABLE 3–4 Cultural Competence Models and Applied Examples for Self-Care		
Model	Attributes	Applied Example in Self-Care
Cultural Competence Continuum (Terry Cross) ³⁴	Cultural Destructiveness <i>Beginning of the continuum and most negative stage</i> • Attitudes and policies support bigotry, racism, discrimination, and exploitation harmful to cultures and patients. • Behavior can be intentional or unintentional. In the Tuskegee study, the U.S. Public Health Service withheld syphilis treatment from African American men.	A health care provider judges patients who demonstrate religious symbols on tattoos, clothing, or jewelry. Staff members often perpetuate the attitude by making judgmental remarks about appropriate attire.
	Cultural Incapacity • Organizations or providers do not have any programs or services to respond to needs of patients from other cultures. • Ethnocentrism often exists in which a dominant culture makes assumptions about	A pharmacy may not carry candles requested by several patients in service area. This lack of response signals failure to recognize the cultural importance of a common, inexpensive, noninvasive adjunct self-care modality (prayer and candles).

Model	Attributes	Applied Example in Self-Care
	other cultures.	
	Cultural Blindness • Organizations or individuals try to remain unbiased. • Assumption is that culture or race makes no difference, that everyone should be treated “equally.” • Organizations have programs in place but do not tailor them to address cultural needs of different groups.	A provider insists on shaking hands and hugging all patients in an effort to fit in and show empathy.
	Cultural Precompetence <i>Skewed toward positive end of continuum</i> • Health care organizations or individuals recognize that cultural differences exist. • Organizations may reach out to cultures by hiring diverse workforce, interpreters, or translators for written materials. • Organizations limit their efforts to several initiatives and may become frustrated with lack of progress.	Providers might be quick to point to an herbal product line available in their pharmacy targeted for a specific cultural group and assume that this action suffices to care for different cultures.
	Cultural Competence • Acceptance and respect for differences among cultural groups is ongoing. • Providers and organizations continually increase their cultural competence knowledge and skills. • Models are implemented to deliver culturally appropriate	Organizations include annual staff training of personnel to better understand the self-care needs of patients from different cultural groups.

Model	Attributes	Applied Example in Self-Care
	care with a true commitment to improve outcomes of patients from diverse cultures. • Providers strive to assess personal cultural biases and beliefs. • Concerted efforts are made to meet and work with people of diverse backgrounds in the community. • Assessments to improve care for different cultures are ongoing.	
	Cultural Proficiency <i>Highest level in the continuum</i> • Organizations and providers have a true commitment to culturally competent practices by engaging in research, evaluating new approaches to care, publishing and disseminating findings, advocating for improvements, and conducting trainings. • Work to achieve cultural proficiency is continual, and the positive impact and the transformation of understanding and engaging different cultures are valued.	Ongoing training for staff and students on community health beliefs and values is provided, with opportunities for community members to assist in training sessions on commonly used self-care modalities, religious beliefs, preferred foods, and other cultural elements.
Cultural Competence Model (Purnell³⁵)	Unconsciously Incompetent Providers do not realize what they do not know about other cultures or the influence of culture across person, family, and community.	A provider encourages influenza vaccine for an individual, not recognizing that the family home is multigenerational and everyone could be vaccinated.
	Consciously Incompetent Providers recognize that they have	A provider realizes that there may be different values about contraception in a

Model	Attributes	Applied Example in Self-Care
	challenges working with persons from diverse backgrounds.	Nigerian culture and takes time to research information about the beliefs.
	Consciously Competent Providers are aware of their effort to work effectively within or across different cultures.	A provider trains the entire staff on cultural touchstones for a new refugee population resettled in the community. Key cultural leaders are invited to help role play and address potential cultural beliefs and practices.
	Unconsciously Competent Providers are more easily able to navigate within a different culture or across new cultures; their approach may seem effortless.	A provider who has worked with Mexican American patients with diabetes over time is able to identify various cultural barriers to self-management.
ASKED Model (Campinha-Bacote ³⁶)	Cultural Awareness Providers explore their own culture and profession through a process of understanding personal biases and assumptions about different cultures.	Providers acknowledge cultural differences in home remedies and self-care treatments commonly used to alleviate cold symptoms, such as chicken soup and hot tea with lemon.
	Cultural Skill Providers have the ability to collect, assess, evaluate, and adapt cultural information from diverse patients to improve care.	In obtaining information about religion and culture in the social history, a provider recognizes that a woman who identifies as Islamic may prefer to have a female provider discuss medication for a yeast infection.
	Cultural Knowledge Process of gaining more information about diverse cultures, values, beliefs, and practices	Providers learn about common herbs and alternative therapies used in the Vietnamese American Buddhist population living in the neighborhood surrounding the pharmacy or clinic.
	Cultural Encounters Providers may have the opportunity to work with one or more patients and families in diverse cultures to enrich their awareness, knowledge, and skills.	Daily clinical practice may include interactions with multiple patients who are Hispanic, so that over time, the importance of family in making decisions about diet and diabetes management becomes evident.
	Cultural Desire Providers are sincerely motivated to grow in their capacity and skill to navigate across cultures.	In addition to working with patients from the large Catholic parish nearby, a Hindu provider volunteers at the parish community and outreach events.

Key: CAM = Complementary and alternative medicine.

Source: [References 34–36](#).

The Cultural Competence Continuum model developed by Terry Cross explores six stages of cultural competence from cultural destructiveness to cultural proficiency.³⁴ As providers and educators gain more experience and develop their skills and knowledge, they may move toward cultural proficiency.³⁴

The Purnell model, which is based in several disciplinary theories (e.g., organizational, family development, religion, political science), describes the interrelationship of several cultural domains such as heritage, family roles, workforce issues, and high-risk behaviors ([Figure 3–1](#)).³⁵ In this model, providers go through a zigzag developmental process, moving from “unconscious incompetence,” wherein they may not realize that they lack knowledge and skills to work in diverse cultures, toward “unconscious competence,” wherein they have a positive attitude and a more developed foundation of knowledge and skills to adapt care in an efficient manner.

Figure 3–1 The Purnell Model for Cultural Competence. (Source: Reprinted with permission from [reference 34](#).)

The model developed by Campinha-Bacote has five primary constructs in the cultural competence process. The first four of these constructs are cultural awareness, cultural knowledge, cultural skills, and cultural encounters.³⁶ Overlapping these constructs is *cultural desire*—a concept that providers are caring and want to gain knowledge and skills to navigate across cultures. In this model, providers also adopt an attitude of *cultural humility*, recognizing that their own culture is not to be construed as the “right” one (ethnocentrism) and striving to maintain a state of lifelong learning about all cultures. Health care providers can use any of these models as a framework for working with patients from diverse cultures and backgrounds and for developing cultural sensitivity.

Barriers to Self-Care

Differences in patients' language and health literacy (educational), access, capacity, and motivation to take care of themselves (personal), and/or perceived health status and confidence to take care of themselves (sociocultural) pose barriers that can apply to self-care. For example, patients' perceptions of the severity of their health condition may influence whether they pursue care. Providers should be able to recognize the various barrier influences that can affect patients' self-care behaviors.

In some instances, the provider may miss small differences in the interpretation of language, gesture, or eye contact. Such omissions can lead to misunderstandings between people of different cultures and the providers they encounter. A provider's lack of cultural sensitivity and linguistic competence may impede the delivery of appropriate care.

Fear and Mistrust of Health Care Providers

Patients' mistrust of health care systems, providers, and information may create barriers to self-care management, including reduced rates of preventive and follow-up care. Patients may feel that providers do not consider their concerns, with the result that their expectations were not met. Some health disparities for minority populations, as historically found in African Americans, American Indians, and other groups, have been associated with discriminatory treatment and systemic racism. Many negative institutionalized health care policies and social aspects of provider–patient relationships remain as barriers to effective care. “Racism is insidious, cumulative, and chronic”; its effects can be felt by patients, providers, and all people in health care organizations. Ongoing mistrust and patients' perceptions, whether real or apparent, can adversely affect patient satisfaction and health outcomes.³⁷

Persons from diverse races and ethnic minority groups also may differ in their perceptions about research and research participation. For example, in some African American and other communities, mistrust of research is firmly entrenched as a result of the Tuskegee study conducted by the U.S. Public Health Service (USPHS) for 40 years, between 1932 and 1972.³⁸ In that study, African American men with (n = 399) and without (n = 201) syphilis were enrolled without informed consent for “free” medical examinations and meals

while researchers monitored the physiologic effects of the disease. Even when penicillin was discovered as a treatment for syphilis, subjects were not informed of the treatment option, nor were they offered the antibiotic. Because of the unethical decisions of the Tuskegee study, many African Americans who are not recent immigrants are unwilling today to participate in clinical trials and other aspects of the medical system. Fear persists that unfair treatment and further abuses will occur.³⁷

Other diverse populations, including women, also have often been underrepresented in clinical research trials. The National Institutes of Health (NIH) National Institute on Minority Health and Health Disparities has a mission to lead scientific research to improve minority health and eliminate health disparities.³⁹ NIH and FDA mandates for inclusion of diverse cultures and minorities in research studies have succeeded in encouraging accountability in research design through stronger commitment to community-based approaches, emphasis on institutional review board approval, and increased federal research funding.^{37,40}

American Indians also have survived a past that includes government policies and wars that damaged their peoples and culture. However, since the Indian Health Service was implemented, American Indian communities are now more protected and have been better positioned to sustain their cultural traditions through family and clan relationships, kinships with homelands, religious ceremonies, and ancient rituals.³⁷

The long and troubled history of American Indians and African Americans with public health services provided by the USPHS or through the Indian Health Service has led these communities to often mistrust providers and health systems. This mistrust perception may be based on multiple aspects, such as⁴¹

- Feelings of prejudice against their ethnic group
- Fear that their best interests are not considered and that they are treated differently from other patients
- Apprehension that their concerns and problems are not heard
- Concern that their traditional medical practices and/or beliefs will not be affirmed and will be called primitive
- Lack of confidence in the health care provider's skills to diagnose and recommend treatments

Other populations also may have perceptions of mistrust derived from sources

in their past history outside the United States.⁴² Individuals and families who have had to seek refugee status may have experienced political oppression or government policies that fostered suspicion or unfair practices. Fears may be centered on deportation for persons who entered the country undocumented, or skepticism may derive from previous experiences using different health care systems or resulting in denial of treatment because of language barriers.

Persons who identify as LGBTQ (Q = Questioning or Queer) also may experience distrust of the health care system and disparities in care, including lower overall health status and higher rates of substance use disorders and mental health illnesses.⁴³ LGBTQ patients face potential stigma and lack of understanding of their particular self-care health needs, as well as exclusive health system practices, including barriers to health insurance or visitation restrictions. Providers may be unsure of appropriate language and preferred names/pronouns (e.g., ze, zie, he, she, they) to use with patients. To provide inclusive care, it is recommended that health care organizations allow all patients to specify their preferred name/pronouns, gender identity, sexual orientation and relationship status on registration forms and other relevant documents and to avoid language that makes assumptions (e.g., using patient names instead of Mr./Mrs./Miss/Ms., asking about a spouse or partner instead of assuming the patient has a husband or wife).⁴⁴ Although LGBTQ individuals experience higher rates of sexually transmitted infections (STIs) and human immunodeficiency virus (HIV) infection than their heterosexual counterparts, health care provider education and medical literature for LGBTQ communities that focus only on STIs and/or HIV infection without inclusion of other health care needs promote perpetuation of stereotypes and biases.⁴⁵

Reducing mistrust of the health care system requires repeated positive encounters over time. Some key practices that health care providers can adopt to foster trusting relationships include one-on-one outreach and frequent personal involvement with the population served. Volunteering and partnering with community leaders, such as clergy, spiritual leaders, or special population advocacy groups, can help to form networks and establish program approval at the earliest stage of the health care planning process.⁴¹

Training of community health workers, or of other lay community health advocates, can be an effective strategy for garnering trust in the community, especially when time and resources are limited. Such community liaisons can help to diffuse health messages, integrate culturally and linguistically diverse

prevention programs, provide information about new health technologies, and provide health screenings in the language and the context best understood by the group under focus. Health care providers should embrace cultural sensitivity training to identify their own potential biases and stereotypes and to gain knowledge to better address patients' feelings of mistrust, improve communication, and create trustful relationships.

Language Barriers

The inability to speak or read English makes it difficult for many patients to communicate with their health care provider or to read instructions on prescription and nonprescription labels that are only in English. Limited English proficiency (LEP) creates a significant barrier to seeking self-care or the advice of a provider when services are only delivered in English. Because of LEP, patients may rely on information from television or magazines written in their language of origin or on the recommendations of family members, relatives, or community leaders. Although many community pharmacies have telephone-based interpreter services available, patients who are making self-care decisions in the aisle of the pharmacy may not be aware of this service and may not request assistance from the provider, who could subsequently offer information via telephonic interpretation.

According to Title VI of the Civil Rights Act, when organizations receive federal funding, they are responsible for taking measures to provide “meaningful access” for services at no charge to persons with LEP. These measures are based on four primary factors related to frequency of contact and importance of contact: the number or proportion of LEP persons in the eligible service population, frequency with which LEP patients come into contact with the program, importance of the service provided by the program, and resources available to the recipient.⁴⁶ The federal interagency LEP website includes mapping tools to gather information about English language proficiency demographics reported at county and state levels. Barriers to care arise when organizations and/or providers (1) do not have available interpreter services; (2) do not know how to work with interpreters; (3) are charging patients for interpretation services; (4) request that patients bring family members or friends as interpreters; and (5) supply signs, forms, and brochures in English only.

Literacy and Health Literacy

Studies have documented a relationship between poor reading skills and poor health.⁴⁷ People who cannot read often hide their limited literacy skills because of shame, embarrassment, low self-esteem, and fear. Without specific attention to this issue, health care providers may overlook this potential source of misinformation concerning self-care products and nonadherence to prescription drugs.

To detect literacy problems, the provider should be sensitive to cues that indicate difficulty with reading. For example, patients may not want to look at the prescription label or patient education material when asked to read information. People who read poorly may never join a group education session. Instead, such patients may prefer one-on-one consultations with their health care providers.

Health literacy, or “the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions,” also is an important skill for self-management and decision making about nonprescription products.⁴⁷ A person may have a high level of reading literacy but not be able to apply a combination of functional skills, such as reading, calculating basic math, and drawing conclusions, to make an informed decision about his or her health.⁴⁷

In different cultures, styles of communication and belief systems can affect health literacy.⁴⁷ Low-level health literacy is more common in minority groups and may be linked to general literacy levels and/or language. Overall low-level health literacy makes it difficult for providers to rely on using existing nonprescription labels, drug information pamphlets, or prescription labels produced by the pharmacy computer systems to give to patients. Through verbal communication with the patient, an interpreter, or an adult family member, providers must ensure that the patient understands the instructions and/or prescription label directions. The prerequisite requirements of the Durham–Humphrey (1951) and Kefauver–Harris (1962) amendments to the Federal Food, Drug, and Cosmetic Act, which the FDA uses in evaluating New Drug Applications for proposed nonprescription drugs, demonstrate the need for improved health literacy.⁴⁸ The criteria for nonprescription drug approval include evidence that (1) patients can recognize and diagnose themselves for the condition specified in the proposed indication, (2) patients can read the

product label and extract the key information necessary to use the drug properly, (3) the drug is effective when used as recommended, and (4) the drug is safe when used as instructed. The consumer must be able to read and understand the information on the label to know the proper dosage, recognize warnings and contraindications, and determine whether contraindications apply.

FDA labeling requirements implemented in 2002 were intended to make it easier for patients to read and understand nonprescription drug labels.⁴⁹ The standard product label for nonprescription drugs, titled “Drug Facts,” has specific sections for active ingredients, uses, warnings, indications for when to use the product, directions, and inactive ingredients (see [Chapters 1](#) and [4](#)). Manufacturers are required to use large print, simple language, and an easy-to-read format on the labels to help patients with product selection and dosage instruction. In addition to these requirements, pharmacists should be alert to the educational needs of all patients, particularly those with poor reading skills or low-level health literacy, buying nonprescription products.

Providers can ensure that patients understand aspects of their condition and their responsibility for self-care by integrating the following tips. First, the provider should never take for granted that the patient can fully comprehend all instructions, whether written or spoken. Patient counseling also should take into consideration the potential for shame related to lack of understanding, so it is especially important to treat the patient with respect. Patient education specialists suggest using the teach-back method to ensure clarity and comprehension of the message. This method involves using phrases such as “Tell me in your own words how you are going to take this medicine.” Gaps in the patient’s interpretation will provide additional opportunities to explain the process again or to correct gaps or misunderstandings using different methods to deliver the message. Education should be followed with presentation of materials such as pictures or demonstration products, and perhaps with follow-up phone calls.

Of note, this approach also may improve adherence to treatment and clinical outcomes.

Sociocultural Framework for Self-Care

Practices

Self-care behaviors have not been well described among different population groups. Factors that influence self-care behaviors can include the patient's understanding of their health in the cultural context of health and attitudes toward taking responsibility for one's own health and illness. Religious beliefs, family and social context, cultural expectations, education and training, and personal experiences affect self-care behaviors. These interpretations are within the foundations of an ethnomedical model of care.^{50,51}

According to Kleinman, the patient's understanding of a disease is based on a "consensus of beliefs, information, and expectations pertaining to the illness that are shared with a social network."^{50,51} This understanding helps the patient interpret healing and sickness. Normative beliefs are generated by social interaction and personal experiences, which may differ completely from a scientific research approach to evidence-based medicine and the use of technology to diagnose and treat patients, which are within the biomedical model of care.^{50,51} For example, some cultures may view hypertension as caused by tension, stress, or worry and may not understand that the disease is the chronic elevation of arterial blood pressure.

Providers who do not consider their patients' beliefs and expectations may encounter resistance to their professional advice. Expecting patients to respond to health care advice solely on the basis of biomedical principles may evoke considerable frustration for both patient and provider. Each patient may have different social support needs and concerns related to making decisions about self-care behaviors and medication use. Providers should recognize the significance of extended family and friends often seen in minority populations' self-care behaviors. For example, a mother with diabetes may be neither able nor willing to modify her dietary intake of certain traditional foods so as not to impose these restrictions on the whole family. Such patients are willing to sacrifice their own health to maintain comfort and convenience for the rest of the family.

Normative beliefs based on the group's experiences also may assist the individual patient in making decisions whether to seek care from the health system or to use CAM. Self-care practices of many cultural groups involve use of home remedies, herbs, massage therapy, acupuncture, or other treatments

that are passed from generation to generation. Communicating within the framework of the patient's culture helps break down barriers while also facilitating trust and understanding between the patient and the health care provider. Through this knowledge, the provider can lead a patient away from harmful practices and provide safe, culturally appropriate alternatives. Subsequently, the provider can develop interventions, even biomedical ones, within the context of the patient's belief system. If traditional self-care practices are not harmful or even are found to be beneficial to the patient, the provider may be able to incorporate them into a monitored and integrated treatment plan.

For example, a patient who is being monitored and treated through Western medicine might also use a folk or traditional healer. Some common healing methods include prayers, massage, and aromatherapy. Because these practices may be harmless and potentially additive to Western medicine, the provider may accept and even encourage their use as found in CAM. It is important to maintain open and consistent communication with the patient, traditional healers, and other health care providers regarding new information on CAM.

Patients and/or their family members are responsible for the day-to-day management of their illness. Consequently, better methods are needed to determine the patient's health-seeking behaviors, informational needs, preferences, and expectations about treatment management approaches. Providers are encouraged to develop a framework for understanding how patients interpret their experiences. Such a framework, according to Kleinman,^{50,51} extends beyond discrete medical episodes of "controlling the biological malfunctioning of disease" to include the psychosocial dynamics of family-based care, healer-patient transactions, spiritualism, shamanic cures, and other important holistic approaches based on the patient's world view. Using this approach can reduce the adverse impact of miscommunication, misinformed decisions, and harmful health behaviors.

General Description of Beliefs in Different Population Groups

Some common themes have emerged in the literature related to chronic illness and self-care behaviors in older adults from African American, American Indian, Asian American, and Latino backgrounds. These self-care behaviors

may be more common among minority groups whose identities are rooted in their home culture and who may feel less identity with Western culture and values.⁵² The following six concepts highlight how self-care practices may be connected to various cultural ideals or beliefs:

1. *Concepts of independence and interdependence.* In Western medicine, independence, self-determination, and autonomy may be linked to increased self-care. Among black persons, particularly women, values of self-reliance and independence are consistent with self-care. Among older American Indians and Hispanics, family needs may supersede the importance of individual health. Messages of self-care in these populations may need to focus on helping the overall family structure. Among older Asian Americans, a mixed phenomenon may occur because of a higher emphasis on self-discipline consistent with self-care, but family needs may also be valued over those of an individual.
2. *Acceptance of intergenerational households.* European American households are less likely than those of other races and ethnic groups to include older family members. When households have several generations living together, different dynamics of social and family support for self-care may exist.
3. *Gender roles within the family structure.* Across cultures, women often are given the role of “health manager” in the family, even if the basic culture of the household is patriarchal. In intact family units, women may have a greater role in influencing self-care practices of the family. When an older married man is widowed, however, he may have a decreased ability to achieve effective self-care, which may be noted especially among black and Hispanic men.
4. *Family traditions related to CAM use.* In general, older adults and immigrants from African, American Indian, Asian, and Latin cultures more often use indigenous or non-Western treatments as part of self-care compared with whites. However, the degree to which these traditions are being passed on to subsequent generations is unclear, and many alternative health practices, including the use of dietary supplements, vitamins, meditation and/or yoga, also are commonly utilized by white people.
5. *Role of friends.* Friends, godparents, and “fictive kin” (very close friends in family-like relationships) can be relied on for support as much as family. For example, in some African American communities, women rely strongly on each other to help provide child care. Hispanics,

American Indians, and Asian Americans also have strong extended friendships that are closely connected to the family.

6. *Religious and spiritual beliefs of different cultures.* The role of God and spiritual healing may influence how persons from a cultural group use and/or accept self-care practices. In some American Indian cultures, physical health is not as important as spiritual or emotional health. In some African American communities, churches have a central role that is sometimes of a familial nature.

Differences in health beliefs and behaviors, as well as the relationship of biological and societal influences, are documented in the literature.²Table 3–5 lists some of the characteristics shared by people of diverse populations in the United States.^{2,53} These characterizations are generalizations. Again, not every member of an ethnic or cultural group may conform to these attitudes and beliefs.

TABLE 3–5 Examples of Cultural Behaviors Among Selected Populations^a

Group (heritage)	General Characteristics
Hispanic	• May actively involve family in health care • May use <i>curanderos</i> and <i>curanderas</i> (traditional healers) • May use home remedies, mostly teas or herbal remedies • May use religious medals for good luck • May believe that health is a matter of “luck” or “fate” • May have an attitude toward recovery that is pessimistic (“fatalism”) • May believe that illnesses are classified as hot and cold, with treatment chosen depending on the classification of the disease
Asian	• May stress the importance of family • May seek balance between forces to define health (<i>yin</i> and <i>yang</i>) • May believe that illnesses are caused by an imbalance of cold and hot forces • May use Eastern medicine, herbal products, Ayurvedic practices (India), or other CAM modalities • May not trust Western medicine
Black (not recent immigrant)	• May stress importance of biological and fictive family • May use home remedies and folk medicine

Group (heritage)	General Characteristics
	• May distrust the health care system because of previous unfavorable experiences • May stress the importance of religion in achieving cure
American Indian	• May use sweat lodges as a means of cure • May use herbal medicine including natural roots • May use prayer for cure of illnesses • May believe that health is a harmony with “Mother Earth” • May use healers (medicine man or woman, shaman)
White	• May have non-nuclear family structures and non-traditional family roles as a result of cohabitation, divorce, and remarriage • May report more pain than people of other races • May have suboptimal health habits including overconsumption of food, often of poor nutritional quality • May have defined (formal) religious practices and a belief in one God and life after death

^a The described behaviors have been observed in these racial and ethnic groups and serve solely as a guide and do not constitute a stereotype.

Source: References 2 and 53.

Additional resource: Halbur KV, Halbur DA. *Essentials of Cultural Competence in Pharmacy Practice*. American Pharmacists Association, Washington, DC. January 2008. Available at: <https://doi.org/10.21019/9781582121130>.

The previous examples are presented to help raise provider awareness of aspects of health behavior they may encounter. Awareness of these issues may help providers to deliver more effective care with increased cultural sensitivity.

Religious beliefs also are important in patients’ acceptance of the diagnosis and self-care treatment advocated by the health care system. A set of beliefs, attitudes, and expectations of illness and treatment based on religion may

cause friction with the health care system and the health care team. For example, a person whose religious background is Jewish, Islamic, or Hindu may have restrictions on the use of certain nonprescription products ([Table 3–6](#)). Consumption of omega-3 fatty acids and other animal-based or gelatin-containing products may or may not comply with strict religious guidelines (kosher or halal) regarding consumption of animal-based products.

TABLE 3–6 Resources for Some Religious and Culturally Based Food and Medication Decisions

Provider	Information Provided	Website
Islamic Food and Nutrition Council of America	Resources on food and items considered to be halal	www.ifanca.org/
Star-K	Approved Medications 2017 (medications considered kosher)	www.star-k.org/ resources_medicine.php
OK.org	Kosher Medicine Lists for Pesach and Year Round	ok.org/consumers/ passover/kosher- medicine-lists-pesach- year-round/
Orthodox Union	Guidelines for Medication–Passover 2019: (Orthodox Union kosher certification)	www.oukosher.org/ passover/articles/ guidelines-medication- for-passover/
Queensland Health	Healthcare Providers’ Handbook on Hindu Patients	www.health.qld.gov.au/ multicultural/ health_workers/hbook- hindu
United States Conference of Catholic Bishops	Information on love and sexuality	usccb.org/beliefs-and- teachings/what-we- believe/love-and- sexuality
Australia Department of Health	Guidance to identify medications and pharmaceuticals of animal origin (while published in Australia – may provide insight for international products) version 2.1 (2019)	www.health.qld.gov.au/ qhpolicy/docs/gdl/qh- gdl-954.pdf

Note: This table does not provide a comprehensive list of resources used by various religions or cultural groups. Rather, it is a guide to explore various beliefs and practices. Individual practices and beliefs may vary.

Key: n/a = Not applicable.

People from different cultures may choose to treat illnesses using different rituals and religious items that are outside the realm of Western medicine. For example, patients who identify as Hispanic may use home remedies or other artifacts recommended by spiritual healers, sometimes called *curanderos*. These healers may use a combination of herbal remedies and religious rituals. When providers are nonjudgmental, they can better understand how and when the patient plans to use drug therapy or another, alternative treatment. Knowing this information can help in determining what previous treatments the patient used or is going to use or whether the potential for major interactions exists between the nonprescription product and the patient's alternative treatment.

Risks of Self-Medication and Suboptimal Responses to Nonprescription Drug Therapy

Limited data are available specifically on the use of nonprescription products among patients of diverse cultural backgrounds, ability levels, religions, and lifestyles. The improper use of nonprescription products places vulnerable populations at an increased risk for adverse drug reactions, drug–drug interactions, and toxic effects from long-term exposure. Therefore, the potential for misuse of drugs that are available for self-treatment may outweigh the benefit–risk ratio in some patients. Increased use of nonprescription products by diverse populations may create another self-care challenge.

Low-income patients are often vulnerable to the harmful effects of overuse of nonprescription products for several reasons. First, patients who are chronically ill and have inadequate health insurance may restrict use of prescription drugs when their costs increase. Many uninsured patients use

nonprescription products as alternatives to prescription drugs simply because of cost. These same patients may seek medical care only for the most urgent symptoms, delaying routine visits to their primary care provider's office. Pharmacists who educate patients on the use of nonprescription products can help prevent delays in seeking medical care. Conditions such as hypertension and hyperlipidemia often are not recognized because of lack of symptoms. Nonprescription products may be used by patients to treat minor symptoms associated with these conditions, such as headache or chest discomfort. The key problem with a suboptimal response to a nonprescription medication is that a more serious condition may not be diagnosed until the patient experiences a complication.

Communication With Culturally Diverse Groups

Collecting and Assessing Patient Information

When interacting with patients from different cultures, providers should use specialized communication skills to gather information about a specific patient's cultural and spiritual health-related beliefs and practices. These communication skills include (1) openness to alternative viewpoints and approaches; (2) routine use of inclusive language (e.g., inquiring about a spouse or partner versus husband or wife, asking about sex or gender identity versus assuming male or female) in gathering demographic information; (3) selfawareness of one's own prejudices and biases; (4) engagement to identify the patient's beliefs, expectations, and barriers to treatment; (5) understanding of how the patient's beliefs and attitudes may influence the treatment plan; and (6) negotiating treatment that is acceptable to both the patient and the provider. Trust is essential to gaining awareness of the issues involved in the interaction, and appropriate language and nonverbal signals and behaviors are crucial to effective communication.⁴¹

One classic model for individual and institutional crosscultural development is *LEARN*, a mnemonic that may be used in clinical encounters.⁵⁴ The steps in the LEARN model are as follows:

- Listen with sympathy and understanding to the patient's perception of

the problem.

- Explain your perceptions of the problem.
- Acknowledge and discuss the differences and similarities.
- Recommend treatment.
- Negotiate a treatment plan that is mutually agreed upon.

In the first step of listening, providers can further assess patients' understanding of their illness by applying another tool, the 4 Cs, as adapted from Kleinman's Patient Explanatory Model (PEM).¹ The 4 Cs frame the following questions for the patient and/or family members, to elicit additional valuable information:

1. "What do you call the problem?" (perception)
2. "What do you think caused the problem?" (beliefs regarding source of illness)
3. "How do you cope with the problem?" (use of CAM or other treatments)
4. "What concerns do you have about the problem or treatment?" (understanding of fears; may also address adherence)

Table 3–7 presents examples of how to use the LEARN model in clinical practice. Other techniques and models have been suggested to improve communication and care in cross-cultural settings (**Table 3–8**).

TABLE 3–7 Models for Communicating With Patients Across Cultures

CRASH

- Consider Culture
- Show Respect
- Assess and Affirm differences
- Show Sensitivity and Self-awareness
- Do it all with Humility

Source: Rust G, Kondwani K, Martinez R, et al. A crash-course in cultural competence. *Ethn Dis.* 2006;16(2 suppl 3):S3–36.

ESTF

- Explanatory model of health and illness
- Social and environmental factors

• <u>T</u>herapeutic contracting (treatment) • <u>F</u>ears and concerns
Source: Betancourt JR, Carrillo JE, Green AR. Hypertension in multicultural and minority populations: linking communication to compliance. <i>Curr Hypertens Rep</i> . 1999;1(6):482–8. doi: 10.1007/BF03215777.
ETHNICS
• <u>E</u>xplanation • <u>T</u>reatment • <u>H</u>ealers • <u>N</u>egotiate • <u>I</u>ntervention • <u>C</u>ollaborate • <u>S</u>pirituality
Source: Levin SJ, Like RC, Gottlieb JE. ETHNIC: a framework for culturally competent clinical practice [special issue]. <i>Patient Care</i> .2000;34(9):188.
RESPECT
• <u>R</u>espect • <u>E</u>xplanatory model • <u>S</u>ociocultural context • <u>P</u>ower • <u>E</u>mpathy • <u>C</u>oncerns and fears • <u>T</u>herapeutic alliance and Trust
Source: Bigby JA, ed. <i>Cross-Cultural Medicine</i> . Philadelphia, PA: American College of Physicians; 2003:20.

TABLE 3–8 Using the LEARN Model: Examples

Listen with sympathy to the patient’s perception: A woman from the African country of Somalia is reluctant to give her mother medication for pain. When asked about this reluctance, she explains that she would prefer to help relieve her mother’s pain through massage.^a

Explain your perceptions of the problem: A pharmacist encounters a patient from Iraq who is experiencing upper respiratory sneezing and coughing and requests an antibiotic. The pharmacist,

who is aware of the wide availability of such drugs without a prescription in Iraq's health care system, explains the differences in pharmacy practice between the two countries and emphasizes the concern among today's health care providers about overprescribing antibiotics, which do not work for viral infections and increase the growth of antibiotic-resistant bacteria. The pharmacist recommends appropriate nonprescription symptomatic therapy, suggests that the patient see a primary care provider, and helps to find an appropriate provider.^b

Acknowledge, Recommend, and Negotiate: A patient from Cambodia complains that her 7-year-old child has had a "fever" for several days. The health care provider has read that the word for "fever" in the Cambodian language may not necessarily mean an elevated temperature. Rather, the term may refer to just not feeling well. The provider clarifies with the mother that the child actually has had a common cold and no elevated temperature.^c Together, they find an appropriate nonprescription therapy to treat the symptoms. The mother agrees with the plan.

^a Data from: Lewis T, Mooney J, Shepodd G. Somali cultural profile. EthnoMed, 2009. Available at: <http://ethnomed.org/culture/somali/somali-cultural-profile>. Accessed May 5, 2019.

^b Source: Regester K, Parcels A, Levine Y. Iraqi refugee health cultural profile. EthnoMed, 2012. Available at: <http://ethnomed.org/culture/iraqi>. Accessed May 5, 2019.

^c Source: Graham EA. Clinical pearl: "fever" in SE Asians. Does it really mean an elevated body temperature? EthnoMed, 1997. Available at: http://ethnomed.org/clinical/culture-bound-syndromes/pearl_fever. Accessed May 5, 2019.

Using Language Assistance and Support

In many instances, a barrier to effective communication may be the patient's inability to speak English. Several websites (Table 3–9) provide tips for providers to work with health care interpreters and with patients who have limited English proficiency, and CLAS standards 5–8 outline a blueprint for organizations in providing communication and language assistance.³

TABLE 3–9 Resources for Developing a More Culturally Competent Health Care Environment

Tips for Using an Interpreter and Linguistic Competency

Collaborating with interpreters: American Speech-Language-Hearing Association www.asha.org/PRPSpecificTopic.aspx?folderid=8589935334&section=Key_Issues

Best practices for communicating through an interpreter: Refugee Health Technical Assistance Center refugeehealthta.org/access-to-care/language-access/best-practices-communicating-

Tips for Using an Interpreter and Linguistic Competency
through-an-interpreter
National standards for culturally and linguistically appropriate services in health and health care: U.S. Department of Health and Human Services, Office of Minority Health thinkculturalhealth.hhs.gov/pdfs/EnhancedNationalCLASStandards.pdf
Limited English proficiency (LEP) resources for effective communication: U.S. Department of Health and Human Services hhs.gov/civil-rights/for-individuals/special-topics/hospitals-effective-communication/limited-english-proficiency/index.html
Cultural Competency Assessments
<i>Health Care Training</i>
Tool for assessing cultural competence training: Association of American Medical Colleges aamc.org/initiatives/tacct
<i>Individual</i>
Cultural and linguistic competence health practitioner assessment: Georgetown University National Center for Cultural Competence clchpa.org
Cultural competence self-test: American Association of Family Physicians www.aafp.org/fpm/2000/1000/p58.html
<i>Organizational</i>
Health care delivery organization: Lewin Group. Indicators of cultural competence in health care delivery organizations: an organizational cultural competence assessment profile. Health Resources and Services Administration, U.S. Department of Health and Human Services; 2002 hrsa.gov/culturalcompetence/healthdlvr.pdf
Assessment of organizational cultural competence: Association of University Centers on Disabilities aucd.org/docs/councils/mcc/cultural_competency_assmt2004.pdf
National Center for Cultural Competence nccc.georgetown.edu/resources/assessments.html
Health Literacy Assessment
<i>Organizational</i>
Health Literacy Pharmacy Organizational Assessment ahrq.gov/professionals/quality-patient-safety/quality-resources/tools/literacy/index.html
Broad Resources for Cultural Competence and Health Disparities

Tips for Using an Interpreter and Linguistic Competency
Office of Minority Health, U.S. Department of Health and Human Services minorityhealth.hhs.gov
Culture, language, and health literacy: Health Resources and Services Administration, U.S. Department of Health and Human Services hrsa.gov/culturalcompetence
Integrating cultural information into clinical practice: Harborview Medical Center, Ethnomed ethnomed.org
Health equity, minority health: Centers for Disease Control and Prevention cdc.gov/minorityhealth/
Ethnogeriatrics: Stanford School of Medicine geriatrics.stanford.edu/

Interpreter services provide a means of addressing a language barrier, but this approach has limitations when only untrained interpreters are available.¹ Problems may arise when family members are used as interpreters because the intimate nature of information conveyed may place participants in an uncomfortable position. An additional issue emerges when a younger family member, sometimes a child, is asked to interpret for older family members, such as parents or grandparents, in a clinical encounter. Putting a child in a position of responsibility is not acceptable and can lead to family conflicts by altering the hierarchy within the family. It also places an undue psychological burden on the child. Accordingly, this situation should be avoided.³

Using family members or untrained personnel to interpret may lead to receiving or transmitting inaccurate information. The health care provider may miss relevant and critical information, or information may be misinterpreted by the interpreter and/or patient. These problems can be avoided with use of only personnel who are trained in medical language interpretation, collaborate frequently with providers, and are familiar with the patient's cultural background. Of note, in some cultures, shared health care decision making with other family members, spiritual leaders, and/or cultural leaders is highly valued, and inclusion of these persons may be beneficial to aiding patient comfort with health care recommendations.¹

Developing a Self-Care Plan

Self-care activities include a range of individual health behaviors such as

health maintenance, use of preventive services, symptom evaluation, self-treatment, interaction with health care providers, and seeking advice through lay and alternative care networks. In general, providers should encourage patients' and their families' participation in self-care behaviors to promote patient empowerment. Unfortunately, some health care providers do not encourage self-care behaviors because they are not aware of appropriately targeted techniques, strategies, and support systems that patients can use.

When assisting patients in their self-care behaviors and self-medication, providers can help to initiate dialogue to support informed decision making. Providers also can participate in health screening programs to identify health risks in the community and can lead health awareness campaigns.

The self-care plan should include the cultural values, behaviors, and beliefs expressed by the patient. The provider must then use this information to develop self-care recommendations and patient education strategies. Communication with other health care providers about the patient's cultural beliefs and preferences is essential. A collaborative approach helps to ensure that all providers are aware of the patient's preferences. For example, when developing a plan of care for the treatment of a self-limiting illness that requires nonprescription drug therapy, providers can synthesize their knowledge and skills by expanding on "negotiating a treatment plan" from the LEARN model. When negotiating a plan, providers can evaluate the following issues:

- Communication styles and needs (e.g., interpreter, family support)
- Patient beliefs and perceptions (as revealed from the PEM and 4Cs) and relevant restrictions related to religion, cultural beliefs, insurance, work environment, socioeconomic position, immigration status, and so on
- Previous treatments (prescription, nonprescription, and CAM modalities) and acceptance of these therapies
- Use of tools to help patient understand and apply recommendation (e.g., medication calendar, pictograms, dosing reminders, pill boxes)
- Appropriate follow-up support (e.g., adverse event, worsening of condition, need to see a provider)

Ensuring Cultural Competence in Health Care

Organizational Commitment

Even the most culturally sensitive, respectful, and competent health care providers will find it difficult to optimize care for patients without organizational commitment, support, and training to work across diverse cultures. CLAS standards provide guiding principles for organizations.³

Organizations that support more culturally competent services should have established policies and infrastructure (e.g., guiding values and principles, recruitment of diverse providers and staff, policies for using interpreters) to support culturally and linguistically authentic, high-quality health care.⁴⁴

Furthermore, such organizations demonstrate a capacity to systematically include feedback from consumers and communities they serve as well as to participate in ongoing self-assessment. Both providers and health system leaders should have a commitment to change, hold a genuine conviction of the significance of the task, and conduct periodic in-depth self-assessments of the beliefs and attitudes of personnel and the institution itself.

Organizational leadership can conduct cultural and linguistic competence self-assessments of the sponsoring institution and the quality of care being provided ([Table 3–9](#)). For example, leaders could form a committee to conduct a baseline self-assessment among department managers, staff members, patients, and community agencies to gain perceptions of the mission, hiring policies, access to interpreters, and community outreach as components of the self-assessment. This process could be evaluated by the committee with recommendations for action. Ongoing organizational support for cultural sensitivity and competency training within the workforce provides a path for continuous improvement. As of 2015, three states had CLAS training legislation (in development or enacted), 11 had state-sponsored implementation activities, and 21 states had both legislation and implementation activities to provide cultural sensitivity training to part or all of the health care workforce.⁵⁵ Other broad resources listed in [Table 3–9](#) may be helpful for learning more about how to improve cultural sensitivity.

Organizations can also evaluate how they serve persons with diverse health literacy skills. The Agency for Healthcare Research and Quality (AHRQ) maintains a website exploring health literacy issues in a pharmacy setting ([Table 3–9](#)).⁵⁶ The AHRQ Pharmacy Health Literacy Assessment tool guides an examination of the physical pharmacy layout, assessment of pharmacy staff, and eliciting feedback from patient focus groups. Recommended educational

materials should be at a sixth-grade reading level or below and use a variety of media to convey a health message.⁵⁷ Creation of a culturally inclusive pharmacy environment can assist with communication and welcome diverse patient groups. Example strategies are increased diversity of persons in photographs used for advertising or education (e.g., with respect to age, race, ethnicity, ability level, or gender expression) and provision of bilingual materials and signage, display of universal symbols, and availability of private counseling areas, and communication aids (interpreter services, special phone, and braille). Pharmacy computer databases should record specific cultural needs and behaviors of the patient. These platforms should include information such as religion, language, preferred pronoun and preferred name, gender identity, special needs or accommodations, and health literacy level.

Cases 3–1 and 3–2 illustrate important aspects of culturally sensitive care in the area of self-care. These cases present examples of issues that may commonly be encountered in community practice.

Case 3–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
Integrate the Patient Explanatory Model (PEM) with the 4Cs ¹ : • What do you call the problem? • What do you think caused the problem? • How do you cope with the problem? • What concerns do	

Relevant Evaluation Criteria	Scenario/Model Outcome
you have about the problem or treatment?	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient comes to the pharmacy asking for help in locating gluten-free selenium supplements. She states that she was advised by her sister in Mexico that selenium could help with "fogginess and feeling tired all the time." She reports that she has noticed markedly increased fatigue and forgetfulness for about 3 months. On further questioning she also reports constipation, weight gain, and dry skin.
PEM: What do you call the problem? (or What do you think you have?)	"I think I have a lot of fatigue."
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	She states that she notes that she often feels cold. She keeps a light sweater with her.
PEM: What do you think has caused the problem?	"I think that I must be low in nutrients. It has been hard to eat well after I retired."
c. Description of the patient's efforts to relieve the symptoms	She has tried homemade bone broth with minimal relief.
d. Patient's identity	Claudia Castañeda de Orta
e. Patient's age, gender,	64 years, female, Hispanic, 5 ft 6 in., 168 lb

Relevant Evaluation Criteria	Scenario/Model Outcome
race/ethnicity, height, and weight	
f. Patient's occupation	Retired
g. Patient's dietary habits	Patient adheres to a gluten-free diet.
h. Patient's sleep habits	She sleeps an average of 7 hours per night but also has been napping in the afternoon lately owing to increased fatigue.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	<i>Osteoarthritis:</i> Glucosamine and chondroitin, turmeric
	<i>Seasonal allergies:</i> Butterbur
	<i>Hypertension:</i> Losartan 10 mg daily; grapeseed and hawthorn extract
	<i>Gluten intolerance</i> (not diagnosed with celiac disease or allergy)
j. Allergies	Seasonal (spring and fall)
k. History of other adverse reactions to medications	None
l. Other (describe) -----	Patient prefers use of "natural products" to medication whenever possible. She does have a primary care physician, whom she sees every year for her annual physical examination. She will consider use of Western medicine for "serious illnesses."
PEM: How do you cope with the problem?	
PEM: What concerns do you have about the problem or treatment?	Patient wants to enjoy retirement and her grandchildren. With the loss of energy, she feels very frustrated.
Assess	

Relevant Evaluation Criteria	Scenario/Model Outcome
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Patient is suffering from fatigue, forgetfulness, dry skin, constipation, cold intolerance, and weight gain, most likely indicative of hypothyroidism.
3. Identify exclusions for self-treatment.	Serious condition with potential for severe sequelae if it goes untreated
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Recommend self-care with drug, nondrug, and/or complementary therapies. (2) Refer the patient to a primary care provider for treatment. (3) Recommend self-care until a primary care provider can be consulted. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Mrs. Castañeda should consult her primary care provider.
6. Describe the recommended therapeutic approach to the patient or caregiver using the LEARN model. ⁵⁴	Apply the LEARN model:
<i>Listen to the patient.</i>	Listen: As described earlier, the health care provider has noted the patient's preference for natural medicine.

Relevant Evaluation Criteria	Scenario/Model Outcome
<i>Explain your rationale.</i>	Explain: “Mrs. Castañeda, I am concerned about your well-being. While you have been using the selenium, it sounds like you have not been feeling better. In fact, it seems that you feel worse.”
<i>Acknowledge the patient's feelings and experience.</i>	Acknowledge: “I recognize how important it is for you to use natural products. I also want to be sure that we are not missing any serious problems. I also hear that you want to have quality time with your grandchildren and enjoy retirement.”
<i>Recommend a course of action.</i>	Recommend: “It seems that your situation is severe and may lead to serious complications such as depression or heart problems if you don’t take care of it. You really need to consult your primary care provider to check some lab values and explore a prescription treatment.”
<i>Negotiate a plan.</i>	Negotiate: “I see that you are taking Losartan, which was prescribed by your primary care provider. I would like to confirm your commitment to seeing your regular provider as quickly as possible. Would you be able to call your provider today?”
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	Treatment with natural products is not recommended until you have been evaluated and diagnosed by your primary care provider.
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	n/a
Solicit follow-up questions from the	“Are there any natural thyroid supplements that I could use instead of prescription medications?”

Relevant Evaluation Criteria	Scenario/Model Outcome
patient or caregiver.	
Answer the patient's or caregiver's questions.	"You may notice supplements available on the shelf that claim to support thyroid health. However, none of these supplements are approved to treat an actual thyroid disorder. Your primary care provider can run blood tests to see how your thyroid is working and then recommend the best treatment for you based on those results. If you wish to also take a natural supplement, after you have seen your primary care provider for treatment, please come back and we can help you choose one that won't interact with your thyroid medication."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Mrs. Castañeda in 1-2 days to ensure that she made an appointment and sought medical care.

Key: n/a = Not applicable.

Case 3-2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
Integrate the Patient Explanatory Model (PEM) with the 4Cs ¹ : 1. What do you call the problem?	

Relevant Evaluation Criteria	Scenario/Model Outcome
2. What do you think caused the problem? 3. How do you cope with the problem? 4. What concerns do you have about the problem or treatment?	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	A mother comes into the pharmacy looking for an over-the-counter senna extract (Castoria) to treat colic in her breastfeeding infant. She was advised by her grandmother that this natural remedy can help with fussiness and abdominal tension by helping to increase the frequency of bowel movements. She reports that for the last few days her baby cries for 1-2 hours a night starting at 6 pm, "like clockwork." She appears distressed and tired and expresses that she may "just need to stop breastfeeding."
PEM: What do you call the problem? (or What do you think is wrong?)	The mother thinks the baby is colicky.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Symptoms are worse in the evening and after nursing. Sometimes the symptoms lessen in severity after the infant passes gas or has a bowel movement.
PEM: What do you think has caused the problem?	The mother states that she feels she is a "terrible mother" and doesn't know how to take care of her baby.

Relevant Evaluation Criteria	Scenario/Model Outcome
c. Description of the patient's efforts to relieve the symptoms	She has tried drinking catnip tea to pass to the infant in her breast milk without noticeable improvement.
PEM: How do you cope with the problem?	The mother states, "I've been drinking herbal tea."
d. Patient's identity	Eden Fenton and infant son Jamal Fenton
e. Patient's age, gender, race/ethnicity, height, and weight	<i>Mother:</i> 32 years, female, African American
	<i>Infant:</i> 6 weeks, male, African American
f. Patient's occupation	Ms. Fenton works in the restaurant industry.
g. Patient's dietary habits	She has no dietary restrictions.
h. Patient's sleep habits	She has had difficulty establishing a sleep schedule since Jamal was born. She reports no more than 4-5 hours of sleep in a 24-hour period for past 6 weeks.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	<i>Mother:</i> Gestational diabetes, controlled with diet; no current medications
	<i>Infant:</i> No known medical conditions
j. Allergies	<i>Mother, infant:</i> None known
k. History of other adverse reactions to medications	<i>Mother, infant:</i> None
l. Other (describe) -----	Ms. Fenton is planning to return to work in 2 weeks and feels "desperate" to control the colic before that date. She wants to use childcare services in the evenings during her shift without being worried that her baby is crying the whole time.
PEM: What concerns do	

Relevant Evaluation Criteria	Scenario/Model Outcome
you have about the problem or treatment?	
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Infant is suffering from symptoms of colic, including predictable bouts of crying without apparent cause occurring in the evening.
3. Identify exclusions for self-treatment.	Excessive, inconsolable crying for more than 3 hours per day may be an indication of a condition that is causing pain or discomfort.
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Recommend self-care with drug, nondrug, and/or complementary therapies. (2) Refer Ms. Fenton to a pediatric care provider for treatment for her baby's symptoms. (3) Recommend self-care until the health care provider can be consulted. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Discourage use of senna and recommend alternative self-care strategies until a pediatric specialist can be consulted to rule out underlying causes of colic (such as reflux).
6. Describe the recommended therapeutic approach to the patient or caregiver using the LEARN model. ⁵⁴	Apply the LEARN model:

Relevant Evaluation Criteria	Scenario/Model Outcome
<i>Listen to the patient.</i>	Listen: The health care provider has noted the patient's stated preference for senna as a natural medicine.
<i>Explain your rationale.</i>	Explain: "Ms. Fenton, senna is a laxative that can be harmful to children under the age of 2 years. Sometimes colic can be a sign of a painful condition, and it would be best to ask your pediatrician to check Jamal to see if a medical problem is causing the crying."
<i>Acknowledge the patient's feelings and experience.</i>	Acknowledge: "I realize how frustrated and even exhausted you must feel."
<i>Recommend a course of action.</i>	Recommend: "In the meantime, I would recommend soothing strategies for Jamal including pacifiers, car rides, walks in a stroller, rocking him in your arms, swaddling, warm baths, soothing sounds, and belly or back rubs. Also, while breastfeeding, consider taking foods out of your diet that may cause problems such as irritation or allergies for your baby. These food items can include nuts, milk products, cabbage, spicy foods, and wheat."
<i>Negotiate a plan.</i>	Negotiate: "Do you have a friend from work, your grandmother, or another family member who might be willing you to help you a couple of nights while you try these changes?"
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"These non-medication options are best, because use of laxatives may lead to severe dehydration and other serious health risks in infants and young children."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	"Soothing and feeding strategies to improve colic may be time-intensive, and it is important to also take care of yourself by taking breaks, talking with people about your feelings, asking for help with meals and housework, exercising, and getting as much sleep as possible."

Relevant Evaluation Criteria	Scenario/Model Outcome
Solicit follow-up questions from the patient or caregiver.	“Would it be better for me to switch to formula and stop breastfeeding?”
Answer the patient’s or caregiver’s questions.	“There is strong evidence that breastfeeding is best for infants, so it is encouraged for at least 12 months whenever possible. Strategies to help reduce colic in breastfed infants include limiting cow’s milk in your diet, ensuring that the baby feeds long enough to empty one breast (to get the richer ‘hindmilk’), and ‘burping’ the baby regularly. Also, it might be helpful to consider joining a mom’s group or La Leche League for additional support.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Ms. Fenton in 1 week to ensure that she made an appointment with the pediatrician.

Key: n/a = Not applicable.

Key Points for Multicultural Aspects of Self-Care

- Cultural and diversity issues may affect patients’ attitudes and behaviors toward health and illness, as well as their acceptance of and adherence to self-care treatment plans.
- Demographic shifts in the U.S. population from age, race, and language to religion, disability status, and other cultural group changes affect the approach and delivery of care to patients.
- Minority populations—including patients from diverse races and ethnic groups, women, people with disabilities, persons who identify with the LGBTQ community, and older adults—have

experienced a range of health disparities. A disproportionately high number of minority-population patients continue to experience increased burden of disease, lower access to care, and higher rates of complications compared with those in other populations.

- Mistrust and fear of the U.S. health care system and providers can prevent some minority-population patients from seeking care. Clinical interactions that are culturally and linguistically sensitive, respectful, and competent can positively affect the quality of care for patients in diverse populations.
- Health care providers should assess and evaluate their own values and beliefs about cultures while acquiring knowledge and skills to deliver effective care for patients from diverse cultures and backgrounds.
- When collecting information from patients, providers should integrate PEM processes to gain understanding of patients' perspectives on causes, treatment, and concerns specific to their illness and overall health status.
- When making a therapy recommendation, providers can apply the LEARN model to listen, explain, acknowledge, recommend, and negotiate a more culturally appropriate self-care plan.
- Providers who can work across diverse cultural groups can support patients in making self-care decisions.

Chapter 4: Legal and Regulatory Issues in Self-Care Pharmacy Practice

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This chapter examines the legal and regulatory aspects of the manufacturing, distribution, labeling, and marketing of nonprescription drug products in the United States. Theories of civil liability, negligence, and breach of warranty also are discussed.

A working understanding of legal and regulatory issues for nonprescription, homeopathic, and dietary supplement products is necessary for today's pharmacist, whose pivotal role in patient counseling on the selection and use of these products continues to expand. Staying ahead of the dynamic and frequently changing myriad of legal and regulatory issues in self-care pharmacy practice is essential for effective communication across the continuum from patients to elected representatives. With appropriate consideration of corresponding legal liability, this practice area constitutes a natural and broad-based opportunity for engaging patients in the clinical process, facilitating communication, and documenting professional services provided. Nonprescription and prescription drugs are regulated differently, but both are held to the same standards for safety and efficacy. Nonprescription medications are actively and stringently regulated by the U.S. Food and Drug Administration (FDA) and the Federal Trade Commission (FTC). For pharmacists and other health care providers, familiarity with these regulations is essential for framing the most helpful responses to patients' questions and concerns about the self-care products they use.

Reflecting formal usage in pharmacy practice, the term *nonprescription* replaces *over-the-counter* (OTC) throughout this book. However, historically and in many publications, as well as in common parlance, these designations are used interchangeably.

History of Self-Care

Self-care has evolved over many decades, from the era of patent medicine, with often expansive promises of benefit including cure as well as purely

fraudulent claims of efficacy, to the current availability of both standard and novel nonprescription therapeutic agents with proven health benefits and cost savings for self-reliant consumers.

In 1906, the Pure Food and Drugs Act¹ prohibited adulteration and misbranding. As a result, many patent medicines (ineffective cure-alls also referred to as nostrums and/or snake oils) were forced off the market. This was followed in 1914 by the Harrison Narcotic Act,² which required prescription-only status for opium and other narcotics. However, this law exempted patent medicine manufacturers if their products contained less than threshold amounts of opium and proved difficult to enforce. In 1938, the Food, Drug & Cosmetic Act (FDCA)³ mandated safety of foods, drugs, and cosmetics, with further standards established in 1951 with the Durham-Humphrey Amendment.⁴

Before enactment of the Durham-Humphrey Amendment, the manufacturer determined whether a product would be a prescription or nonprescription drug. Confusion ensued, with some manufacturers of a particular product marketing the drug as a nonprescription medication and other manufacturers of the same drug specifying prescription-only status. There was no FDA listing of prescription medications, and the manufacturer's interpretation of the FDA regulations of prescription versus nonprescription status was often arbitrary. If FDA disagreed with a product status determination, its sole recourse for remedy was to sue the manufacturer for misbranding.⁵ Many nonprescription products were marketed without approved New Drug Applications (NDAs) and were considered "grandfathered" drugs.

In 1937, ingestion of a preparation of sulfanilamide using diethylene glycol as a solvent resulted in the deaths of more than 100 people from kidney failure. At that time, the toxicity of diethylene glycol was unknown. The product was sold over the counter. The event prompted the passage of the 1938 FDCA. However, even the tragedy related to the nonprescription sale of sulfanilamide (as "Elixir of Sulfanilamide") in 1937 did not clarify when a medication should be available without a prescription, and the confusion continued until 1951 with passage of the Durham-Humphrey Amendment. This amendment provided the statutory basis for two classes of drugs in the United States: prescription and nonprescription. The FDCA required that in the absence of a medical need to restrict distribution, nonprescription availability is the default status for FDA-regulated products.

The next legislation that affected nonprescription drugs was the Kefauver-Harris Drug Amendments of 1962, which required proven efficacy for marketed products, including nonprescription drugs.⁶ To address this requirement, the focus was on a review of prescription drugs through a Drug Efficacy Study Implementation (DESI) program. Subsequently, in 1972, FDA instituted the “OTC Review” process, described later in the chapter (see “The Nonprescription Drug Review Process”).

In 1991, FDA created the Division of Nonprescription Drug Products within the Office of Drug Evaluation in the Center for Drug Evaluation and Research (CDER). FDA has issued more than 25 guidance documents for nonprescription medications. Although not legally enforceable, these directives describe FDA’s current opinion on a topic and should be viewed as recommendations. A listing of guidance documents pertaining to nonprescription drugs, with brief content summaries, is presented in [Table 4–1](#).

Table 4–1 FDA Guidance Documents	
Document	Description
Maximal Usage Trials for Topically Applied Active Ingredients Being Considered for Inclusion in an Over-the-Counter Monograph: Study Elements and Considerations (2019)	Document describes need for maximal usage trials to support an FDA determination that a topically applied product for OTC use is GRASE.
Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use (Draft) (2018)	Document describes performance studies required for validation of sterility and disinfection tests for FDA approval to enhance infection control with these devices.
Innovative Approaches for Nonprescription Drug Products (Draft) (2018)	Document presents two additional approaches for FDA approval of additional conditions for OTC products when the Drug Facts label alone is not sufficient for this purpose.
Policy Regarding Quantitative Labeling of Dietary Supplements Containing Live Microbials (Draft) (2018)	Document explains that FDA will use enforcement discretion for probiotics labeled in colony-forming units rather than weight.
Enforcement Policy- OTC Sunscreen Drug Products	Document explains FDA’s enforcement approach and certain products and claims (e.g. prevents skin cancer) for which it will no

Document	Description
Marketed Without an Approved Application (2018)	longer exercise enforcement discretion.
Drug Products Labeled as Homeopathic (Draft) (2017)	Document refers to FDA's enforcement priorities for homeopathic drugs, none of which have undergone FDA approval or OTC Review.
Gluten in Drug Products and Associated Labeling Recommendations (Draft) (2017)	Document includes voluntary gluten labeling statement for oral OTC drug products (including those applied inside the mouth or near the lips) and its placement outside the Drug Facts label.
Child-Resistant Packaging Statements in Drug Product Labeling (Draft) (2017)	Document provides labeling recommendations regarding child-resistant packaging statements.
Recommended Statement for Over-the-Counter Aspirin-Containing Drug Products Labeled With Cardiovascular Related Imagery (2017)	Document discusses that FDA will not take enforcement action against aspirin manufacturers who include imagery (e.g., heart image, electrocardiography graphic) if the label includes a statement advising patients to consult with their health care provider before using the product for cardiac indications.
Recommended Warnings for Over-the-Counter Acetaminophen Containing Drug Products and Labeling Statements Regarding Serious Skin Reactions (2017)	Document provides recommendations for label warnings about serious skin reactions on acetaminophen products.
Nonprescription Sunscreen Drug Products-Format and Content of Data Submissions (2016)	Document provides further details regarding processes FDA will use to determine if a sunscreen is GRASE.
Nonprescription Sunscreen Drug Products-Safety and Effectiveness Data (2016)	Document details the quality/manufacturing and clinical/nonclinical and postmarketing safety data needed to establish that a sunscreen is GRASE.
Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use (2016)	Document provides guidance for 510(k) submissions for blood glucose test systems for home use by lay persons.
Sunscreen Innovation Act: Withdrawal of a 586A Request or Pending Request & 586C(c) Advisory Committee Process	Two guidances regarding processes FDA will use to determine if a sunscreen is GRASE and should be added to the OTC sunscreen drug monograph.

Document	Description
(2016)	
Organ-Specific Warnings: Internal Analgesic, Antipyretic, and Antirheumatic (IAAA) Drug Products for Over-the-Counter Human Use—Labeling for Products That Contain Acetaminophen (2015)	Document covers alternative allowable language for acceptable liver warnings for products in view of the fact that some IAAA products have maximum daily doses of acetaminophen of <4 g.
Over-the-Counter Pediatric Oral Liquid Drug Products Containing Acetaminophen (2015)	Document covers standardization of concentration to 160 mg/5 mL in view of dosing errors from multiple concentrations. The package must include a dosage delivery device. Dosing directions should be provided in milliliter units only.
Nonprescription Sunscreen Products—Content and Format of Data Submissions to Support a GRASE Determination Under the Sunscreen Innovation Act (SIA) (2015)	Document covers format and content of information needed for 586A requests.
Self-selection Studies for Nonprescription Drug Products (2013)	Document provides recommendations for conducting studies to assess the ability of consumers to apply drug labeling information to their personal health situation to make correct nonprescription purchases.
Labeling and Effectiveness Testing: Sunscreen Products for OTC Human Use (2012)	Document provides information to assist industry to comply with labeling and testing requirements for ultraviolet A and B radiation protection for nonprescription sunscreen products.
Labeling for Bronchodilators: Cough, Cold, Allergy, Bronchodilator, and Asthmatic Drug Products for OTC Human Use (2012)	Document provides information to help industry comply with additional warnings on bronchodilator products (i.e., Asthma Alert and revised indications, warnings, and directions).
Toll-free Number Labeling and Related Requirements for Over-the-Counter and Prescription Drugs Marketed With Approved Applications (2012)	Document provides requirements for toll-free number for ADR reporting (not for medical advice) for products approved pursuant to a monograph process and contact for those approved pursuant to an approved application.

Document	Description
Time and Extent Applications for OTC Drug Products (2011)	Document explains what information is required for submission of a TEA to show that the product has been used “to a material extent” and “for a material time.”
Topical Acne Drug Products for OTC Use—Revision of Labeling and Classification of Benzoyl Peroxide	Document covers addition of benzoyl peroxide as a GRASE active ingredient for nonprescription acne products with new warnings, directions, and labeling requirements.
Label Comprehension Studies for Nonprescription Drug Products (2010)	Document covers recommendations on conducting label comprehension studies.
Organ-Specific Warnings: Internal Analgesic, Antipyretic and Antirheumatic Drug Products (2010)	Document covers labeling requirements for warnings regarding potential liver injury and stomach bleeding.
Postmarketing Adverse Event Reporting for Nonprescription Human Drug Products Marketed Without an Approved Application (2009)	Document covers minimum elements and format for ADR reports and how and where to submit reports.
Labeling of Nonprescription Human Drug Products Marketed Without an Approved Application: Questions and Answers (2009)	Document explains the standardized labeling content and format for products not marketed pursuant to an NDA or ANDA in a Q&A format.
Labeling OTC Human Drug Products—Small Entity Compliance Guide (2009)	Document explains the standardized labeling content and format.
Labeling OTC Human Drug Products—Questions and Answers (2009)	Document clarifies, in Q&A format, the standardized labeling content and format.
Labeling OTC Human Products Updating Labeling in RLDs and ANDAs (2002)	Document assists manufacturers of nonprescription drugs marketed via an ANDA or those holding RLDs to comply with the standardized labeling content and format.
Guidance for Over-the-Counter Human Chorionic Gonadotropin (hCG) 510(k)s (2000)	Document covers pregnancy test kit 510(k) medical device approval and patient labeling requirements.

Document	Description
Labeling of OTC Human Drug Products Using a Column Format (2000)	Document describes how more than one Drug Facts box can be used for each side of a package to allow for the use of columns.
Enforcement Policy on Marketing OTC Combination Products (1984)	Document covers policy regarding marketing of combinations of ingredients.
General Guidelines on OTC Drug Combination Products (1978)	Document describes rules for combinations permitted for marketing. Within each monograph, combinations are detailed: Category I ^b ingredients from <i>different</i> therapeutic categories may be combined to treat different symptoms concurrently in certain circumstances. Category I ingredients from the <i>same</i> therapeutic category should not be combined if they have the same mechanism of action.
Upgrading Category III ^a Antiperspirants to Category I (1978)	Document details the studies required to bring Category III antiperspirant ingredients into Category I.

^a Category III drugs are considered to have insufficient evidence to prove safety and/or effectiveness.

^b Category I drugs are considered to be GRASE.

Key: ADR = Adverse drug reaction; ANDA = Abbreviated New Drug Application; FDA = U.S. Food and Drug Administration; GRASE = generally recognized as safe and effective; OTC = over-the-counter; Q&A = question-and-answer; RLD = reference-listed drug; TEA = Time and Extent Application.

The Food and Drug Modernization Act of 1997⁷ expanded FDA's authority over nonprescription drugs in establishing inactive ingredient labeling requirements. This act preempted states from establishing state-specific labeling requirements when federal requirements exist. In the United States, nonprescription drug manufacturers and distributors are represented by the Consumer Healthcare Products Association (CHPA) (formerly the Proprietary Association and, subsequently, the Nonprescription Drug Manufacturers Association).

Over the past 20 years, legislative and regulatory changes pertaining to nonprescription drugs have been implemented, including standardized labeling with the *Drug Facts* format, additional final monographs (as discussed later under “The Nonprescription Drug Review Process”), prescription-to-nonprescription switches for drugs never marketed before, and a mechanism for drugs marketed in foreign countries to be considered for the OTC Review process. In 2014, the Sunscreen Innovation Act (SIA) provided an alternative process for the review of safety and effectiveness of nonprescription sunscreen active ingredients, a category considered as drugs by FDA.⁸ Most recently, FDA has sought input from stakeholders and the public to improve the regulatory processes for nonprescription drugs.

Nonprescription Drugs: Approval and Regulatory Processes

Definition of Nonprescription Status

Nonprescription medications, by definition, may be used without medical supervision. A drug can be marketed as a nonprescription product if it can be used by a consumer guided by the product label such that the consumer can self-diagnose, self-treat, and self-manage the condition requiring attention and if no health care provider is needed for the safe and effective use of the product.⁹ The drug also must have a low potential for abuse and misuse, and the benefits of nonprescription availability must outweigh the risks.⁹ A state may not allow a prescription drug to be sold as other than prescribed, but a state may restrict a drug with nonprescription status under federal law to prescription status.¹⁰ In *Whitehall Labs v. Wilbar*,¹¹ the court upheld a Pennsylvania law requiring a prescription for Primatene tablets, which was a nonprescription drug by federal rules, finding the Pennsylvania law to be consistent with tenets of consumer protection. Similarly, in *Northwest Corp. v. Oregon Board of Pharmacy*,¹² the court upheld the state’s decision to establish prescription status for ephedrine.

Some nonprescription medications also are available as prescription drugs. In such cases, a determination has been made that the medication is safe for nonprescription use in certain dosages or dosage forms, or for specific indications but not for others. Examples are ibuprofen, for which the 200 mg

dose is nonprescription for pain but higher dosages and strengths are prescription-only for such conditions as arthritis; meclizine, which is a prescription drug for vertigo but a nonprescription medication for nausea with motion sickness; and nicotine products, which have nonprescription status in gum, lozenge, and patch formulations but prescription-only status for inhaled and nasal products.

The FDCA prohibits the simultaneous marketing of the same active ingredient in both a prescription drug product and a nonprescription drug product unless a “meaningful difference” exists between the two that makes the prescription product safe only under the supervision of a healthcare practitioner.¹³ Recently, FDA withdrew the Abbreviated New Drug Applications (ANDAs) for PEG3350 laxative products that were prescription versions of the nonprescription drug, determining there was no “meaningful difference” between the products. The ANDA holders sought review of FDA’s decision by the D.C. District Court, claiming that the duration of therapy differs.¹⁴ The court concluded that there was no “meaningful difference” between the prescription version’s recommended use for 2 weeks or less and the nonprescription version’s recommended use for no longer than 7 days.

The Nonprescription Drug Review Process

On May 11, 1972, FDA announced a review of nonprescription products marketed between 1938 and 1962 that were not covered under an NDA. Rather than review the more than 300,000 products,¹⁵ FDA divided them into categories according to intended therapeutic effect and active ingredients. It then assigned 17 different panels of experts to review each category (e.g., internal analgesics) and each of the more than 700 listed ingredients for safety and effectiveness. Ingredients were assigned to one of three categories: Category I, generally recognized as safe and effective (GRASE); Category II, not GRASE; or Category III, insufficient evidence to prove safety and/or effectiveness (i.e., further information is needed to show safety and efficacy and classify as Category I or II). The panels also considered the first prescription-to-nonprescription (also referred to as “Rx-to-OTC”) switches, such as those for diphenhydramine and hydrocortisone. Panel deliberations were published in the *Federal Register*, with a comment period followed by a proposed rule and, finally, formal monographs, also published in the *Federal Register*, detailing the dosages and labeling requirements for each ingredient.

Manufacturers of products containing ingredients in Category II were required to either reformulate or remove those products from the market. However, banned products could continue to be sold until the inventory was depleted from the pharmacy or wholesaler stock. In some cases, consumers were actually harmed by banned products (e.g., with quinine-induced renal failure) that continued to be sold.¹⁶

For those ingredients placed in Category III, manufacturers were given more than 15 years to conduct necessary studies or to reformulate their products with Category I ingredients. Other manufacturers simply removed the products from the market promptly, primarily because of the prohibitive costs of studies in view of the product sale history. Some regulators thought that the 15-year grace period was too long, and in *Cutler v. Kennedy*, several consumers sued to have Category III ingredients removed from the market.¹⁷ To take advantage of Category III classification without fear of regulatory action, a manufacturer must provide timely notification of, and initiate, testing.¹⁸ In *Cutler v. Kennedy*, the court held that the OTC Review required removal of Category III ingredients after the final monograph was published, to prevent exposure to unsafe or ineffective drugs. Consequently, many products were removed from the market, and others were reformulated. Some products were moved from one category to another on the basis of research data regarding safety and efficacy.

After more than 40 years, the OTC Review process continues to be applied for new ingredients, amendments to monographs, unfinished monographs, and switches. (Of note, at present, several monographs have not yet been finalized and are in “tentative final” or stayed status.) This public rule-making process is documented by publication in the *Federal Register*, with a corresponding comment period, for each of the three phases: (1) Advance Notice of Proposed Rulemaking, (2) Tentative Final Monograph, and (3) Final Monograph. These monographs in final form are then codified in the Code of Federal Regulations (CFR), where they can be found in 21 CFR parts 331–358.

Pathways to Nonprescription Status

Two mechanisms exist for licensing and commercial marketing of nonprescription drug products: NDA and the drug monograph. Today, if a manufacturer follows the monograph process, it need not obtain FDA approval for the product. Monographs are tantamount to “recipe books” that specify the

active ingredients, dosages, and formulations, as well as the labeling and conditions whereby nonprescription drug ingredients are GRASE-compliant. For products that fall outside the monograph specifications, the manufacturer will need either to pursue an NDA,¹⁹ petition to amend the monograph, or modify the product to comply with the monograph specifications.

New agents that are not included in an OTC Review monograph must be regarded as new drugs. For new sunscreen agents, for example, FDA had taken the position that these are constituted of new ingredients requiring an NDA. Under the 2014 SIA, an alternate process known as a 586A request for review of sunscreens was established. In 2015, FDA published four draft guidance documents regarding scientific testing required for determination of GRASE status for a sunscreen and the timelines for FDA review.^{20–23} Examples of nonprescription medications that have required NDAs for a switch from prescription-to-nonprescription status are oxybutynin, ibuprofen, budesonide, and fluticasone nasal spray.

Various types of NDAs can be submitted for marketing of a nonprescription drug:

- Prescription-to-nonprescription switches effected using an NDA or NDA supplement (e.g., omeprazole, nicotine gum, orlistat)
- “Direct-to-nonprescription” (acetaminophen, nicotine lozenge)
- NDA deviation (for new nonprescription products that differ only slightly from monograph products) (rarely used)²⁴
- ANDA used for switching a generic drug to nonprescription status (e.g., loratadine).

A product containing an ingredient new to the nonprescription marketplace is regulated under the NDA process under section 505(b)(1) of the FDCA, such as for a prescription-to-nonprescription switch NDA. An NDA can be used to request approval of a nonprescription drug product that deviates from monograph specifications. The product can be marketed only with the exact formulation and labeling approved by FDA. To make a change, the manufacturer must submit an NDA supplement. Nonprescription products also can be approved by means of a 505(b)(2) application, in which data from previous safety and efficacy testing not conducted by or for the applicant may be used, or using an ANDA under section 505(j) of the FDCA.²⁵ These applications are confidential, but a fee is required. Nonprescription products approved through the NDA route receive a period of exclusivity whereby no

other versions can appear on the market. A comparison of the NDA and monograph routes for nonprescription drug approval is detailed in [Table 4–2](#).

Table 4–2 Comparison of New Drug Application (NDA) and Drug Monograph Regulatory Approval Pathways	
NDA	Monograph
Premarket approval	No premarket approval
Confidential	Public
Drug product-specific	Applies to all products with the ingredient
Potential for marketing exclusivity	No exclusivity
Application filing fees	No filing fees
GMPs apply	GMPs apply
Clinical development required	No clinical development required

Key: GMPs = Good manufacturing practices.

Two mechanisms are available for amending a drug monograph: a Citizen Petition²⁶ and a Time and Extent Application (TEA).²⁷ A Citizen Petition can be used to request an amendment or repeal of conditions covered in a monograph at any stage. However, the Citizen Petition is limited to pre-1975 marketing conditions—that is, active ingredient, dosage form, or indication. For petitions, the product cannot be marketed until FDA approves the petition.

A TEA can be used to request that applicable drug products be considered for inclusion in the OTC Review monograph system.²⁷ A TEA is submitted for drug products that can meet the statutory standard of marketing to a “material extent” and “for a material time.” This scenario is defined to encompass the following: drug products initially marketed under an NDA in the United States after 1972; drug products without any U.S. marketing experience; or those not GRASE (i.e., not meeting monograph specifications) in the original OTC Review but for which additional data are now available. The conditions must have been marketed for nonprescription purchase and for at least 5 continuous

years in the same country in sufficient quantity. Several sunscreen ingredients, such as amiloxate and bisoctrizole, have used the TEA process to reach the U.S. market.

Consumer behavior studies and label comprehension studies are often used to assess whether consumers can appropriately use the product on a nonprescription basis. Because no learned intermediary (i.e., the prescriber) is involved, as for prescription products, such data often are needed to support a switch from prescription to nonprescription status.

It also is mandatory for nonprescription drug manufacturers to register their establishments and list their drug products with FDA.²⁸ Additionally, FDA may require in vivo or in vitro finished-formulation testing (e.g., dissolution tests for enteric-coated and sustained-release products).

Prescription-to-Nonprescription Switch

Since the mid-1970s, FDA has switched more than 100 ingredients, dosages, or indications from prescription to nonprescription status ([Table 4–3](#)). Switch decisions are made by FDA with the advice of advisory councils. Consumers can benefit from prescription-to-nonprescription switches because they broaden access to important medications. In addition, the nonprescription versions usually are cost-effective for consumers and third-party insurers. A survey found that consumers save up to \$750 million a year as a result of using nonprescription cough and cold medications that once were available only by prescription. The same study demonstrated that physician visits for the common cold dropped by 110,000 a year between 1976 and 1989, suggesting that access to nonprescription products contributed to a reduction in office visits.²⁹

Table 4–3 Select Prescription-to-Nonprescription Switches^{a,b}

Purpose/Class of Drug	Drug Name^c	Year of Switch
Allergic rhinitis	Xyzal Allergy 24HR Tablets (levocetirizine)	2017
	Children’s Xyzal Allergy 24HR Oral Solution (levocetirizine)	
	Rhinocort Allergy Spray (budesonide)	2015

Purpose/Class of Drug	Drug Name^c	Year of Switch
	Flonase Allergy Relief (fluticasone propionate)	2014
	Nasacort Allergy 24 HR (triamcinolone) (nasal spray)	2013
	Nasalcrom (cromolyn sodium)	1996
Analgesic/antipyretic	Motrin Migraine Pain, Advil Migraine Liqui-gels (ibuprofen)	2000
	Excedrin Migraine (aspirin/caffeine/acetaminophen)	1998
	Children's Motrin	1995
	Aleve (naproxen)	1994
	Advil, Nuprin (ibuprofen)	1984
Analgesic/decongestant	Advil Congestion Relief (ibuprofen/phenylephrine)	2010
	Children's Advil Cold (ibuprofen/pseudoephedrine)	2002
	Aleve Cold & Sinus (naproxen/pseudoephedrine)	1999
	Advil Cold & Sinus (ibuprofen/pseudoephedrine)	1989
Anthelmintic	Pyrantel pamoate	1986
Anticandidal	Monistat 3 (miconazole nitrate 4%)	1998
	Vagistat-1 (tioconazole)	1997
	Gyne-Lotrimin 3 (clotrimazole)	1996
	Monistat 3 (miconazole nitrate 2%)	1996
	Femstat 3 (butoconazole nitrate)	1995
	Monistat 7 (miconazole nitrate)	1991
	Gyne-Lotrimin, Mycelex-7 (clotrimazole)	1990
Antidiarrheal	Imodium Advanced	1997
	Imodium A-D (loperamide)	1988
Antihistamine	Allegra (fexofenadine HCl)	2011

Purpose/Class of Drug	Drug Name^c	Year of Switch
	Children's Zyrtec Allergy and Children's Zyrtec Hives Relief (cetirizine), syrup and chewable tablets	2007
	Claritin tablets, reditabs, and syrup (loratadine)	2002
	Tavist-1 (clemastine fumarate)	1992
	Doxylamine	1987
	Diphenhydramine HCl	1985
	Drixoral (dexbrompheniramine maleate)	1982
	Tripolidine	1982
	Chlorpheniramine maleate	1976
Antihistamine eye drop	Zaditor	2006
	Alaway	2006
Antihistamine and decongestant or antitussive	Allegra D (fexofenadine/pseudoephedrine)	2011
	Zyrtec D (cetirizine/pseudoephedrine)	2007
	Claritin-D 24 Hour	2002
	Drixoral Plus (dexbrompheniramine maleate/chlophedianol HCl)	1987
	Actifed (pseudoephedrine/triprolidine)	1985
Acid reducer/PPI	Nexium 24HR (esomeprazole magnesium)	2014
	Prevacid 24HR (lansoprazole)	2009
	Prilosec OTC (omeprazole)	2003
	Pepcid Complete (famotidine/calcium carbonate/magnesium hydroxide)	2000
	Zantac 75 (ranitidine)	1995
	Pepcid AC (famotidine)	1995

Purpose/Class of Drug	Drug Name^c	Year of Switch
Anorectal vasoconstrictor	Ephedrine sulfate	1980
	Epinephrine hydrochloride	1980
	Phenylephrine hydrochloride	1980
Antiemetic	Diphenhydramine HCl	1987
Antidandruff	Nizoral (ketoconazole)	1997
Antihistamine	Pataday Once Daily Relief (olopatadine HCl, 0.2%)	2020
	Pataday Twice Daily Relief (olopatadine HCl, 0.1%)	2020
Antimicrobial	E-Z Scrub (povidone/iodine sponge)	1987
Antipyretic	Hydrocortisone (>0.5%–1%)	1991
	Hydrocortisone	1979
Cold sores	Abreva (docosanol)	2000
Decongestant	Afrinol Repetabs (pseudoephedrine, timed-release)	1982
	Oxymetazoline	1976
	Pseudoephedrine	1976
	Xylometazoline	1976
Dental rinse	Acidulated phosphate fluoride	1980
	Sodium fluoride; stannous fluoride	1980
Emergency contraception	Plan B One Step (levonorgestrel)	2009
	Plan B (levonorgestrel)	2006
Expectorant/ decongestant	Mucinex D ER Tablet	2004
	Mucinex DM ER Tablet	2004
	Mucinex ER Tablet (guaifenesin)	2002
Hair regrowth	Rogaine Extra Strength (minoxidil)	1997

Purpose/Class of Drug	Drug Name^c	Year of Switch
	Rogaine (minoxidil)	1996
Laxative	MiraLax (polyethylene glycol)	2006
Ocular vasoconstrictor/ decongestant	Lumify (brimonidine tartrate)	2017
	Zaditor (ketoprofen)	2006
	Naphcon A, Opcon A, Ocuhist (pheniramine/naphazoline)	1994
	Vasocon A (antazoline phosphate/naphazoline)	1994
	Ocuclear (oxymetazoline HCl)	1986
Oral anesthetic	Dyclonine HCl (solution, suspension, lozenge)	1982
Overactive bladder	Oxytrol for Women (oxybutynin)	2013
Pediculicide	Nix (permethrin)	1990
Poison ivy protection	Ivy Block (bentoquaram)	1996
Sleep aid	Advil PM (ibuprofen/diphenhydramine)	2005
	Diphenhydramine (HCl and monocitrate)	1982
	Doxylamine succinate	1978
Smoking cessation	Commit (lozenge)	2002
	Nicotrol TD	2002
	Nicorette (gum)	1996
	Nicotrol, Nicoderm CQ (patch)	1996
Sunscreen	Anthelios SX (Ecamsule/avobenzone/octocrylene)	2006
Topical analgesic	Voltaren (diclofenac sodium gel)	2020
Topical antifungal	Lamisil Derm Gel	2006
	Lotrimin Ultra (butenafine HCl)	2001
	Lamisil AT (terbinafine HCl)	1999

Purpose/Class of Drug	Drug Name ^c	Year of Switch
	Lotrimin AF (clotrimazole)	1989
	Miconazole	1982
Weight loss aid	Alli (orlistat)	2007

^a Complete listing can be found at <http://www.chpa.org/Switch.aspx>.

^b There were no switches from January 1, 2018 through April 1, 2019.

^c When a brand name is listed, the switch was effected using the NDA process. Key: NDA = New drug application; PPI = proton pump inhibitor.

Among the first products to be switched to nonprescription status was ibuprofen for the treatment of pain in 1984. In a few cases, a drug that was available as a nonprescription product was returned to prescription status, an example being metaproterenol sulfate. FDA itself initiated the switch for metaproterenol—a decision that was met with great opposition from physicians and pharmacists.³⁰ Of note, however, FDA considered that selfdiagnosis and self-treatment of asthma with nonprescription metaproterenol may delay physician visits in patients with asthma. Furthermore, a nonprescription product must not require routine medical examinations or laboratory testing, and it was for this reason metaproterenol was returned to prescription status. However, exceptions exist for grandfathered drugs—that is, those available before the FDCA of 1938. This is the reason why Asthmanefrin (racedrine) is available over the counter for temporary relief of mild respiratory symptoms of bronchial asthma. An additional requirement for nonprescription status is that the condition must be one that a patient can self-diagnose, thus keeping products like acyclovir for genital herpes or statins for hypercholesterolemia from being switched to nonprescription status.³¹ Additional issues for acyclovir pertained to increasing resistance to the drug. Similarly, histamine type 2 receptor (H₂) blockers cannot be labeled for use with ulcers, because the patient's symptoms may mask the presence of gastric cancer.³²

Products may be switched from prescription to nonprescription status by any of three routes:

1. Submitting a supplemental NDA (applies to a particular product)
2. Petitioning the FDA (may be filed by interested parties such as manufacturers, health insurance companies, associations, or pharmacy benefit managers)
3. Amending the drug monograph (applies to all products with the ingredient)

The supplemental NDA route is the most commonly used for prescription-to-nonprescription switches, because unlike with the other two routes, the proceedings are confidential and allow for 3 years of marketing exclusivity. The exclusivity is an incentive for status switching of medications for which patents are about to expire, with ensuing generic competition. The supplemental NDA route is used if the manufacturer is planning to switch the prescription drug without a change in the previously approved dosage form or route. However, if the manufacturer intends to convert some but not all of the indications to nonprescription status, an NDA must be filed. If the manufacturer intends to market a new product whose active substance, indication, or dosage form has never been nonprescription, either an original NDA (505)(b)(1) or 505(b)(2) is required. After a drug goes off patent, anyone can file a 505(b)(2) NDA to switch the drug to nonprescription status. Additional efficacy studies may be required in these situations or when the nonprescription population differs from the population used to support the original NDA (e.g., with ibuprofen, for which the nonprescription indications include pain, fever, and dysmenorrhea but the prescription indications are osteoarthritis and rheumatoid arthritis). Label comprehension studies also may be required. However, comparative studies with other agents are not required.

The second switch mechanism is to file a formal request with FDA. This occurs by a Citizen Petition, which must be accompanied by data demonstrating safety and efficacy. In one instance, a managed care organization successfully petitioned FDA to switch several nonsedating antihistamines to nonprescription status in an effort to save money in plan beneficiary reimbursement. Most insurance plans do not cover nonprescription medications.³³ Additionally, Medicaid and Medicare programs often do not pay for nonprescription products. In the case of the nonsedating antihistamines, the manufacturers objected to any switch to nonprescription status, because

they stood to lose revenue if the agents became nonprescription drugs. Profitability of a drug when sold by prescription versus over the counter has a profound effect on whether or not nonprescription status will be sought.

The third switch mechanism is to amend the monograph. A process exists to request amendment or repeal of conditions covered by nonprescription drug monographs. Companies may need to file a complete (not supplemental) NDA to request approval of a nonprescription drug that deviates in any respect from a monograph description. In some instances, FDA itself has decided to allow self-use, as with hydrocortisone and diphenhydramine. The respective monographs were then amended to add these drugs.

In some cases (e.g., ibuprofen, naproxen), a partial switch for nonprescription status occurs whereby some doses become nonprescription whereas others remain prescription. In other instances, two different preparations of a product at the same dose may be marketed as both prescription and nonprescription drugs (e.g., cimetidine 200 mg tablets, loperamide 2 mg capsules). In such cases, the prescription and nonprescription versions may not resemble each other in appearance. Additionally, the indications may differ between the nonprescription and prescription versions (e.g., proton pump inhibitors are nonprescription drugs for heartburn but are prescription-only medications for peptic ulcer disease).

Safe Use of Nonprescription Drugs

Adulteration and Misbranding

A nonprescription drug is *adulterated* if it contains a substance that may make the product harmful to consumers under customary conditions for use; if it contains any filthy, putrid, or decomposed substance; if its container is composed of a harmful substance; or if it is manufactured or held under unsanitary conditions. All nonprescription drug manufacturing must adhere to *good manufacturing practices* (GMPs). Failure to follow GMP requirements may result in adulteration of a nonprescription drug preparation.³⁴

A nonprescription medication is considered *misbranded* if its labeling is false or misleading, if it does not bear the required labeling information, or if the container is made or filled in a deceptive manner. *Labeling* refers to all labels

and other printed, written, or graphic matter on or accompanying a product.

FDA is authorized to inspect nonprescription drug manufacturing facilities, in a capacity similar to its enforcement powers regarding prescription drugs.³⁵ It can then use administrative enforcement tools such as issuing warning letters or requesting a product recall, or it may seek judicial enforcement by means of a civil injunction, criminal penalties, or product seizure. FDA can request but not mandate a recall of nonprescription drug products.³⁶ However, if a manufacturer fails to recall a product pursuant to such a request, FDA may apply other enforcement options such as injunction, seizure, or criminal prosecution.³⁷ Once a manufacturer agrees to recall a product, FDA conducts a health hazard evaluation (HHE), classifies the recall, as described next, and notifies the manufacturer of the classification.³⁶

Three recall categories have been defined. For a Class I recall, a reasonable probability exists that the use of, or exposure to, a violative product will cause serious adverse health consequences or death. For a Class II recall, use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences, or the probability of serious adverse health consequences is remote. For a Class III recall, use of, or exposure to, a violative product is not likely to cause adverse health consequences. Additionally, a recall can extend to the manufacturer, wholesale, retail, or consumer level. Depending on the class or level of recall, the manufacturer's notification can be to direct accounts, such as wholesalers, or to pharmacies, or to the general public by way of the FDA website or media coverage. For recalls at the consumer level, the patient may return the nonprescription product to the place of purchase for a refund. Pharmacists can advise patients about the recall and recommend alternative products to replace the recalled product. Additionally, in the event of a recall, manufacturers provide a toll-free number for consumers to obtain additional information. FDA has a recall audit program to ensure that the recall has been effective.^{36,37} For example, in 2011 FDA mandated changes to dosing instructions for many pediatric (infants and children) acetaminophen products. Immediately upon this 2011 labeling change, acetaminophen products actually in commerce became ineligible for sale. They were subject to a recall owing to their nonmonograph status.

Adverse Drug Reaction Reporting

In 2004, a dietary supplement ephedra (i.e., ma huang) was linked to stroke,

arrhythmias, and death. The product was banned from the U.S. market. Of importance, the incident prompted the mandatory reporting of serious adverse events for dietary supplements and nonprescription drugs.³⁸ The 2006 Dietary Supplement and Nonprescription Drug Consumer Protection Act mandated reporting of serious adverse drug reactions (ADRs) by dietary supplement and nonprescription drug manufacturers.³⁹ Before this act, ADR reporting was required only for nonprescription drugs marketed pursuant to an NDA or ANDA. Manufacturers should notify FDA of all serious ADRs (Table 4-4) by submitting an Individual Case Safety Report (ICSR) on FDA form 3500A, together with a copy of the medication label, via either mail or telephone-transmitted facsimile (fax), within 15 business days of receipt. The ADR also may be reported online using the MedWatch reporting form. Consumers may report adverse reactions from nonprescription products using the MedWatch online form or by mail or fax using FDA form 3500B.

Table 4-4 Defining Criteria for Serious Adverse Events

- Death
- Life-threatening
- Hospitalization (initial or prolonged)
- Disability or permanent damage
- Congenital anomaly/birth defect
- Required intervention to prevent permanent impairment or damage (including device placement)
- Other serious important medical events (e.g., allergic bronchospasm requiring treatment in an emergency department; seizure that does not result in hospitalization)

For nonprescription products approved under an NDA or ANDA, the requirements are the same as for prescription products approved under these applications—that is, 15-day, periodic, and annual reports of both serious and nonserious ADRs. All ADR reports must be retained by the manufacturer for a 6-year period. For prescription products, labeling warnings often are included in the prescribing information to inform prescribers even when a causal relationship has not been definitively established; however, only clearly documented, clinically significant, and important warnings are required for nonprescription products.³⁹

The Dietary Supplement and Nonprescription Drug Consumer Protection Act

also requires that a manufacturer of nonprescription products marketed under a monograph review process must place “responsible person” contact information (i.e., domestic address or phone number) on its labels for consumer reporting of ADRs. The responsible person is defined as the manufacturer, packer, or distributor whose name appears on the label. For nonprescription products marketed pursuant to an NDA or ANDA, a toll-free number is required. If the company does not have a tollfree number, the label may include FDA’s toll-free MedWatch telephone number. However, enforcement of this provision has been problematic. Additionally, consumers may report adverse events to FDA at www.safetyreporting.hhs.gov.

ADRs have led to various FDA actions including requiring additional warnings, MedWatch Safety Alerts (e.g., for methemoglobinemia resulting from benzocaine sprays, gels, or liquids applied topically or to gums), category reclassification (e.g., from I to II), request for a recall, or market removal (e.g., of phenylpropanolamine).⁴⁰ Two recent FDA Safety Alerts were prompted by ADRs reported for nonprescription medical devices and dietary supplements that resulted in patient deaths. FDA warned that biotin, especially at dosages in hair and nail supplements, may interfere with laboratory testing. One patient taking high levels of biotin died when a cardiac troponin assay gave falsely low test results.⁴¹ In 2019, FDA warned against use of previously owned test strips (e.g., for glucose or international normalized ratio) or those not authorized for sale in the United States. These products are often sold online.⁴²

Labeling

FDA regulates nonprescription drug labeling. FDA reviews nonprescription drug labels for products marketed under an NDA. Nonprescription products must be labeled with adequate directions for patient use, with accommodation for persons with low-level reading comprehension, without the need for medical consultation. The labeling must be “likely to be read” and “likely to be understood” by the “ordinary individual.” All labels must be in English. However, manufacturers may include a toll-free number for Spanish-speaking consumers to call with inquiries.

Since 1999, the content and format requirements for nonprescription drug labeling have been standardized and specific.⁴³ FDA has even provided guidance on font size for the label, which must be in 6-point type or larger.⁴⁴ The label must appear on the outside container or wrapper, or may be the

immediate container label if packaging does not include an outside container or wrapper, and begins with a Drug Facts panel. It must further include active ingredient(s), purpose(s), use(s), warning(s), directions, other information, inactive ingredients, and frequently asked questions (if relevant).⁴⁵ Inactive ingredients must be listed in alphabetical order and appear on the outside container. Flavors and fragrances may be listed as “flavors” and “fragrances,” respectively.⁴⁵ Trade secret ingredients may be listed as “and other ingredients.” Incidental ingredients present at insignificant levels need not be identified, unless the omission would constitute a failure to reveal a material fact.⁴⁵ (See [Figures 4-1, 4-2, and 4-3.](#))

Figure 4-1 Drug facts labeling outline. (Source: [Reference 44.](#))

Figure 4-2 Drug facts labeling sample 1. (Source: [Reference 44.](#))

Figure 4-3 Drug facts labeling sample 2. (Source: [Reference 44.](#))

Drug Facts warnings may include but are not limited to the following specific phrases and topics: “for external/rectal/vaginal use only”; Reye syndrome warning; allergic reaction warning; flammability warning; choking warning; alcohol warning; sore throat warning; dosage warning; “do not use” warning; “ask a doctor if you have”; “ask a doctor or pharmacist before you use”; “stop use and ask a doctor if”; pregnancy/breastfeeding warning; “keep out of reach of children”; and “contains phenylalanine.” Drug Facts rules detail how to group warnings and how to bullet-list them. In addition, other rules specify what information should appear on the *principal display panel*, which is defined as “that part of the label that is most likely to be displayed, presented, shown, or examined under normal and customary conditions of display for retail sale.”⁴⁶

The labeling permitted for each nonprescription ingredient is detailed in the

monograph. Minor changes are permitted, provided that the content is truthful and the language not misleading. Additionally, repackagers of nonprescription products must comply with the same labeling requirements as those for manufacturers. FDA takes action if label claims are false or misleading. Jurisdiction extends to all labels and labeling in any media, including websites and social media.⁴⁷ NDA ingredients are not found in the monograph, because only the NDA filer is eligible to market these products. Therefore, no rationale exists for providing information for other manufacturers, because they must still go through the ANDA process once the patents expire.

Manufacturers of nonprescription products must warn of foreseeable risks. A voluntary “Flag the Label” program has been adopted by nonprescription drug manufacturers to alert consumers of changes in currently marketed products or labels. *Significant changes* are defined as (1) expansion or limitation of the claims, (2) modification of the dosage level, (3) change in active ingredients or directions for use, (4) new warnings or contraindications, and (5) any other significant new information. The “flag” should be carried on the label for at least 6 months after such a change is made.

An example is product *line extensions*, that is, new products with altered features such as flavors, ingredients, or dosage forms. Line extensions for which product names share the same root name with a suffix or other modifier are prone to patient confusion and errors. FDA reviews and approves proposed trade names for nonprescription products that are approved under the NDA or ANDA process. When products are switched from prescription to nonprescription status, the product may keep its name or use a new name. For partial switches, such as when only one strength formulation is switched to nonprescription status, a new name is usually selected for the nonprescription version. Another example of a change requiring a “Flag the Label” warning is a change in active ingredients. Such was the case when kaolin and pectin were replaced by bismuth subsalicylate in the antidiarrheal Kaopectate.

Some monographs (e.g., for antacid, antiflatulent, topical antifungal, antiemetic, and cough and cold products) contain professional labeling for health care professionals not included in the nonprescription drug labeling for consumers. The professional labeling is located in the nonprescription monograph. For example, the professional labeling in the monograph for nonprescription antiflatulence products contains additional indications for

postoperative gas pain or use in endoscopic examination.⁴⁸

Packaging

Most oral, nasal, otic, ophthalmic, rectal, and vaginal nonprescription medications must be tamper-resistant as required under the Federal Anti-Tampering Act and implementing regulations.^{49,50}

- *Tamper-resistant* refers to a feature of the product packaging that is created to resist access to the product.
- *Tamper-evident* packaging is characterized by features that make previous unauthorized access to the product easily detectable by the prospective consumer. Exceptions include dermatologics, dentifrices, and insulin.
- Tamper-resistant packaging is defined as “an indicator or barrier to entry which if breached or missing can reasonably be expected to provide visible evidence to consumers that product tampering has occurred.”⁴⁹

This requirement was in response to the 1982 case of tampering with and adulteration of Extra Strength Tylenol capsules, resulting in several deaths in Chicago. A tamper-resistant warning statement must be placed on the package and be clearly visible to alert consumers. The statement also must advise consumers not to purchase the product if the tamper-evident features are breached or missing.

Nonprescription products must bear an expiration date, which is determined by appropriate stability testing. However, a nonprescription product is exempt from this requirement if its label does not specify any dosage limitations and if the medicine is stable for at least 3 years.

Under the Poison Prevention Packaging Act (PPPA),⁵¹ child-resistant packaging is required for some nonprescription products commonly available in the home, such as aspirin, acetaminophen, ibuprofen, and methyl salicylates, and for any product switched from prescription to nonprescription status.⁵² The complete list of products that require child-resistant packaging may be found at 16 CFR §1700.14. The Consumer Product Safety Commission (CPSC) has authority for enforcement of the PPPA. Manufacturers have the option of offering one size of a product with a non-child-resistant closure. The

label for this product must specify “this package for households without young children.” However, if that size happens to be the most popular size (e.g., bottles of 100 tablets), the manufacturer also must market that size in child-resistant packaging.

For nonprescription drugs approved via an application (e.g. NDA, ANDA), FDA reviews data related to container closure systems. However, FDA does not approve or review individual products under the monograph system and therefore does not review data related to container closure systems. Even though no process has been defined for ensuring that such nonprescription products meet CPSC standards for child-resistant packaging, manufacturers that have data to demonstrate this safety feature may include a child-resistant packaging statement (e.g. “child-resistant package” or “this package is child-resistant”) on the labeling.

Advertising

FTC regulates advertising of nonprescription drugs, devices, and dietary supplements and prohibits false advertisements, which are defined as those that are misleading in a material respect.⁵³ There is no “fair balance” requirement for benefits versus warnings or contraindications. Advertisements must be supported by the level of data in the manufacturer’s files that the ad wording communicates. For example, if the advertisement states that “pharmacists and doctors recommend” the product, then tests, recommendations, and/or studies must substantiate this statement. A “reasonable basis” standard is applied, meaning that a manufacturer must have objective evidence to support a claim before running an advertisement.^{54,55} In *Warner Lambert Co v. FTC*, the claims for Listerine in the prevention, cure, and symptomatic alleviation of the common cold were found not to be substantiated, and the company was required not only to stop the advertisement but to run corrective advertisements.⁵⁶ In addition to corrective advertising, in other cases FTC has required a manufacturer to conduct at least two clinical trials to substantiate advertising claims.⁵⁵

The National Advertising Division of the Council of the Better Business Bureaus investigates complaints from consumers, competitors, or other parties regarding the truth and accuracy of nonprescription drug advertisements and may escalate the matter to the attention of FTC. Additionally, a manufacturer may file private lawsuits against competitors for false claims in advertising,

packaging, and labeling through Section 43(a) of the Lanham Act.⁵⁷

FDA has indirect authority over advertising of nonprescription drugs. Advertising claims not included in OTC Review monographs may be subject to agency regulatory action under the misbranding provisions of the FDCA.⁵⁸ Additionally, FTC is empowered to issue cease-and-desist orders against false, deceptive, or misleading advertisements of nonprescription drugs. FDA and FTC often act in tandem in reviewing nonprescription drug promotion and have issued joint warning letters to companies that their advertising violates both the FDCA and the FTC Act.

Third Class of Drugs

A little over a decade after passage of the Durham-Humphrey Amendment, various organizations began to advocate for an additional or third class of medications. This intermediate class of drugs would be available without a prescription, but a pharmacist would be required to be involved with the sale. **Table 4–5** shows drug classification in 10 countries. As can be seen, the two-tier system of prescription and nonprescription status in the United States is unique. In fact, the United States and South Africa are the only two countries without such a third class of drugs.

Table 4–5 Drug Classification in 10 Countries			
Country	Prescription	Pharmacist/Pharmacy Class	Nonprescription
United States	x		x
Australia	x	x	x
Canada	x	x	x
Denmark	x	x	x
France	x	x	
Italy	x	x	
Germany	x	x	x
United Kingdom	x	x	x

Country	Prescription	Pharmacist/Pharmacy Class	Nonprescription
Sweden	x	x	x
Switzerland	x	x	x
Netherlands	x	x	

The availability of an intermediate or third class of drugs in the United States, as elsewhere, could be expected to be of considerable benefit in terms of both quality and costs of health care. As a relatively recent example, after the introduction of statins, an important drug class in combating modern diseases, a switch from prescription to nonprescription status would have been not only appropriate but also highly effective in optimizing health care outcomes. With pharmacists involved in the monitoring and education of patients, it is probable that costs, whether economic or health-related (e.g., associated with ADRs), would have been curtailed if these agents had been more readily available as an option for early intervention. An intermediate class of drugs also could be used for those nonprescription products with a potential for abuse or those requiring closer monitoring by a pharmacist.

What is the expected role of pharmacists in this scenario? A major consideration is that a tracking system to capture ADRs would be required. Previous concerns have been the time burden such tracking would place on pharmacists and the likelihood of increased costs. The benefits would be obvious, however, when the medication has a potential for abuse or requires closer monitoring or is a first-in-class agent for a new indication.

Pharmacy associations, the National Consumer League, and other consumer groups favor a third or transition class of drugs. By contrast, CHPA, retail industries, senior citizen groups (for whom former prescription drugs typically would no longer be covered by insurance), and medical groups oppose a third class of drugs. FDA has traditionally opposed a third class of drugs, but in 2012 the agency declared an intent and held a public meeting to clarify parameters for novel switches to nonprescription status. This initiative was termed *Nonprescription Drug Safe Use Regulatory Expansion* (NSURE). Under NSURE, FDA would, for certain common diseases, allow prescription drug products to be available on a nonprescription basis through the use of newer technologies

(e.g., smartphone applications, point-of-care kiosks) or other conditions for safe use (such as pharmacist interventions).⁵⁹ Under NSURE, certain monitoring mechanisms for prescription-to-nonprescription-switch drugs would be allowed, with the proviso of “conditions of safe use.” To date, the criteria have not been established, and the conceptional framework is still in development. However, NSURE has the future potential to increase filings for switches of prescription products that traditionally have been outside the realm of traditional switch candidates, such as first-in-class agents for new indications. Of importance, as a “condition for use,” pharmacist interventions under NSURE would undergo definitive expansion with respect to consultation in recommending nonprescription medications.⁶⁰

FDA has emphasized that NSURE was not intended to create a so-called third class of drugs but rather would operate within the existing two classes. Thus, in accordance with the two-tier system in the United States, medications can either be prescription-only or sold in the local convenience store, with no middle ground.⁵⁹ Aside from the economic interests of the opposers, FDA has been reluctant to establish a third drug class, citing reasons that the current two-class system works and that evidence that a third class would improve public health is insufficient for action.⁶¹ These arguments fall short, however, because as discussed further on, strong evidence indicates that a de facto third class of drugs has a tremendous impact on improving public health.

Since 2006, emergency contraception products for women have been nonprescription. Additionally, several attempts have been made to allow nonprescription sales of oral contraceptives. Studies have shown that women in the United States are very interested in access to oral contraceptives without a prescription, that women can accurately identify contraindications to use of oral contraceptives with simple checklists, and that nonprescription contraception would increase use, with consequent reductions in unintended pregnancy rates.⁶² Thus far, however, every attempt to change the status of oral contraceptives to nonprescription has been met with strong opposition from “pro-life” groups.⁶³ Because an OTC Review monograph for oral contraceptives is lacking, a manufacturer would have to demonstrate product safety and consumers’ understanding of the labeling. Health insurers are required under the Affordable Care Act⁶⁴ to cover the costs of prescriptions for contraceptives. If contraceptives are moved to nonprescription status, insurers would be less likely to pay for them. Removal of this coverage is a disincentive for a change to nonprescription status. Currently, oral contraceptives are

available from pharmacists in several states (e.g., Tennessee, Washington) and Washington, DC, under collaborative practice agreements with licensed prescribers and in other states (e.g., Oregon, California) through direct pharmacist prescribing.^{65,66} However, oral contraceptives remain as prescription products in these scenarios, with pharmacists given additional authority to initiate access to these products via protocol or to prescribe them directly. Although California has no age restrictions, in Oregon female patients younger than 18 years of age must have a previous prescription from a physician or pharmacist. Several states are considering similar legislation. Alternatively, oral contraceptives could be a candidate for an intermediate or third class of drugs.

In 2007, FDA signaled a possible change in its opposition in calling a meeting to obtain comments about creation of a “behind-the-counter” class of drugs.⁶⁷ Unfortunately, the Government Accountability Office (GAO) report issued from that meeting concluded that the experiences in other countries provided little insight into the likely effect of a behind-the-counter class in the United States.⁶⁸ As recently as 2012, FDA announced it was considering creation of a class of nonprescription drugs that could be made available to patients “under conditions for safe use,” which may potentially include pharmacist intervention.⁶⁹ Hearings were held, with the same groups in opposition to the concept. However, no progress has been made moving forward on the concept since then.

De Facto Third Class of Drugs

Certain prescription-status products are already supplied to patients without a prescription, but consumer access to them is restricted: They are available only “behind the counter”—that is, only by expressly asking a pharmacist for them, thereby creating a de facto third class of drugs. This group includes a small number of exempt narcotic combination products placed in Schedule V (e.g., codeine, available without a prescription in several states such as Oklahoma and Washington),⁷⁰ pseudoephedrine (see [Chapter 11](#)), NPH and recombinant (R) U-100 insulin, syringes and needles, and naloxone. Federal requirements for Schedule V medications sold without a prescription are found in [Table 4–6](#).

Another example of voluntary restricted access is that for dextromethorphan, a cough suppressant. Although dextromethorphan is not a Schedule V medication, it is an opioid derivative with psychoactive properties, with the

potential for abuse. Accordingly, drug manufacturers and retailers have imposed state-specific voluntary age restrictions on its purchase, making the drug far less available to teens looking for a hallucinogenic “high.”⁷¹

Table 4–6 Federal Requirements for Schedule V Medications

Feature	Specific Requirement(s)
Schedule V definition	• Codeine preparations: limited to 200 mg/100 mL or 100 g • Dihydrocodeine, ethylmorphine, opium preparations: limited to 100 mg/100 mL or 100 g • Diphenoxylate: limited to 25 mg/25 mcg atropine sulfate • Diphenoxin: limited to 0.5 mg/25 mcg atropine sulfate
Age and personal identification requirement	• Purchaser must be 18 years of age. • Identification is required when pharmacist does not know purchaser.
Seller requirement	• Dispensed only by pharmacist or intern
Medication limitations	• Not more than 240 mL (8 ounces) of any such controlled substance containing opium • Not more than 120 mL (4 ounces) of any other such controlled substance • Not more than 48 dosage units of any such controlled substance containing opium • Not more than 24 dosage units of any other such controlled substance may be dispensed at retail to the same purchaser in any 48-hour period.
Documentation requirement	• Bound record book containing: ◦ Purchaser’s name and address ◦ Name and quantity of medication ◦ Date ◦ Name or initials of dispensing pharmacist
Stricter law prevails	• No state or local law requires a prescription to dispense.

Additionally, in an increasing number of states, pharmacists have been given prescriptive authority to dispense a limited number of prescription-only products without a medical prescription. The first state to allow this provider role was Florida, where pharmacists can prescribe medications listed on a formulary that consists of fluoride- or lindane-containing products, some topical anti-infectives, antihistamines and decongestants, and products recommended by an FDA advisory panel for transfer to nonprescription status but pending FDA action.^{72,73} Currently, six states—Montana, New Mexico, North Carolina, North Dakota, Oregon, and California—give pharmacists midlevel practitioner status, allowing them to initiate and modify drug therapy pursuant to a collaborative practice agreement with a physician.⁷⁴ In 2013 and 2016, laws in California and Oregon, respectively, took effect that allow pharmacists to prescribe oral contraceptives to women 18 years and older.⁷⁵ In California, the professional scope of practice for pharmacists was expanded to include the following⁷⁶:

- Prescribing nicotine replacement therapy, which normally requires a prescription
- Prescribing medications for travel health purposes (e.g., scopolamine patches)
- Mandating tests to monitor and maintain drug therapy for patients with comorbid conditions such as diabetes, hypertension, and hyperlipidemia

Other states are considering similar legislation.

Pharmacists, who constitute the most accessible health professional interface between the community and the health care system,⁷⁷ are ideally positioned to provide overdose education and to expand access to naloxone. Most states have laws that permit, under certain circumstances, any ordinary person to obtain naloxone without a prescription at a pharmacy.^{78,79} However, not all pharmacies carry it. Limited availability of this lifesaving drug, coupled with increased demand, drug shortages, and limited competition among naloxone manufacturers and resultant price increases, has resulted in direct action by FDA to make naloxone available over the counter. In January 2019, FDA took the unprecedented step of proactively creating model labeling via Drug Facts label templates and conducted patient comprehension studies to support OTC naloxone nasal spray and injectable products.⁸⁰

Abuse of Nonprescription Medications

A list of nonprescription medications that have been abused, along with legislative and regulatory initiatives to curb such abuse, is presented in [Table 4–7](#). In protecting the public from abuse of nonprescription medications, pharmacists have a key role to play.

Table 4–7 Anti-Abuse Measures for Various Nonprescription Medications^a

Medication	Effect(s)/Use	Legislative/Regulatory Action
Dextromethorphan	Dissociative effects; altered mental status; intoxication	Many products reformulated to omit ingredient; in some states, behind-the-counter sale only (e.g., New York, Utah)
Pseudoephedrine (also applied to ephedrine, but sale limits differ)	Precursor used in manufacture of methamphetamine	Combat Methamphetamine Epidemic Act of 2005 (logbook of sales; limits daily purchase amounts to 3.5 g, with 30-day limit of 9 g and mail order 30-day limit 7.5 g) Schedule V in some states (Illinois, Iowa, Kansas), Schedule III in others (Oregon, Mississippi) ^b
Class V Controlled Substances (e.g., cough syrups)	Opioid abuse	See Table 4–5
Laxatives	Anorexia; electrolyte imbalances; gastrointestinal complications	
Loperamide ^c	Cardiotoxicity; ventricular arrhythmias; QT and QRS prolongation	None
Nonprescription antihistamines; dimenhydrinate	Intoxication; stimulant effects including euphoria and hallucinations	None

^a DEA's Office of Diversion Control website provides more detailed information

regarding sale limits and recordkeeping requirements:
https://www.deadiversion.usdoj.gov/pubs/manuals/pharm2/appendix/appdx_g.htm.

^b Source: U.S. Department of Justice Drug Enforcement Administration. Combat Methamphetamine Epidemic Act 2005. Title VII of USA Patriot Improvement Reauthorization Act of 2005. Pub L No. 109-177. 109th Congress. March 9, 2006. Available at: <http://www.deadiversion.usdoj.gov/meth/index.html>.

^c Source: U.S. Food and Drug Administration. Drug Safety Communication: FDA warning about serious heart problems with high doses of the antidiarrheal medicine loperamide (Imodium) including abuse and misuse. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm504617.htm>. Accessed May 14, 2019.

Key: DEA = Drug Enforcement Agency.

From Cosmetic to Drug: Crossing the Line

FDA's authority over cosmetics is less comprehensive than its authority over other FDA-regulated products. Laws that pertain to cosmetics are the FDCA, specifically, the adulteration and misbranding provisions⁸¹; the Poison Prevention Packaging Act; and the Fair Packaging and Labeling Act.⁸² There are no requirements for manufacturer registration, premarket notification, ingredient safety testing, product listing, monographs, GMPs, or ADR reporting.⁸³ Cosmetic manufacturers may voluntarily decide to register with FDA and report ingredients in their products. FDA does not have authority to require a manufacturer to recall a cosmetic product from the marketplace.⁸⁴ Regulation is under the FDA Center for Food Safety & Applied Nutrition, specifically, the Division of Colors and Cosmetics.

In an early opinion, FDA stated that some cosmetics are also nonprescription drugs. Such products must meet the regulatory requirements (including labeling and packaging) for both cosmetics and drugs. Additionally, many legal precedents are in place for products that have crossed the line from cosmetic to drug—so-called cosmeceuticals.⁸⁵ Early cases involved wrinkle removal products for which the product claims included strong therapeutic implications.^{86,87} Other cases involve cosmetic product claims that establish the product as intended to treat or prevent disease or otherwise affect the

structure or functions of the human body. Often it is not the ingredient used in the product but rather the labeling claims content that determines whether the product is considered a cosmetic or a drug. Examples are claims that products will restore hair growth, reduce cellulite, treat varicose veins, or regenerate cells. The mere presence of ingredients in low or inactive levels, that is, below those specified in an OTC Review monograph, also does not make a cosmetic a drug. Examples of cosmetic products that also may be drugs are listed in [Table 4–8](#).

Table 4–8 Cosmetics That Also May Be Drugs

- Topical antimicrobial products (e.g., soaps containing antimicrobials)
- Skin protectants
- Sunscreen products
- Antiperspirant products
- Skin-bleaching products
- Nail hardeners
- Teeth whiteners with bleach
- Indoor and oral tanning preparations
- Hormone creams
- Eye wrinkle creams
- Wrinkle eradicators or antiaging creams

If a cosmetic is also a drug, the active ingredients must be listed first, followed by other ingredients, except flavors and fragrances, in descending order of predominance, on the product package. The “principal display panel” on the label must include the net quantity, name and place of the manufacturer, the declaration of ingredients, and any warning statements. Specific content that determines when a cosmetic should be classified as a drug includes (1) claims to cure, mitigate, treat, or prevent a disease; (2) claims to effect major changes in the structure of the body, or in a major bodily function; and (3) presence of a compendium-listed ingredient intended to serve medicinal purposes.⁸⁸

Compounding Nonprescription Drugs

At one time, nonprescription products were routinely compounded as needed. Although explicit guidelines on compounding nonprescription medications

are lacking, and the pharmacy compounding provisions of the Food and Drug Modernization Act of 1997 do not directly address nonprescription drugs, pharmacists should rely on guidance established for compounding prescription medications. Pharmacists should not compound any medication for nonprescription use that is intended to be used pursuant to a prescription or one that has not been approved for nonprescription use. Additionally, as with prescription medications, pharmacists should not compound large quantities of nonprescription medications that are essentially copies of commercially available nonprescription drugs.⁸⁹ A summary of regulatory requirements for nonprescription drugs is presented in [Table 4–9](#).

Table 4–9 Summary of Nonprescription Drug Regulations	
Feature	Component(s)
Labeling	• Drug Facts format • Regulated by FDA • Inactive ingredients in alphabetical order
ADR reporting	• Required for both OTC Review monograph- and NDA-approved nonprescription drugs
Manufacturing	• GMPs
Advertising	• Regulated by FTC
Packaging	• Tamper-resistant • Child-resistant
Marketing	• By NDA • By monograph route

Key: ADR = Adverse drug reaction; FDA = U.S. Food and Drug Administration; FTC = Federal Trade Commission; GMPs = good manufacturing practices; NDA = New Drug

Application.

Nonprescription Homeopathic Drugs

Homeopathy is a system of alternative medicine based on the practice of treating symptoms of a disease with substances that produce symptoms of the disease in healthy subjects (i.e., on the basis of the principle “like cures like”). Nonprescription homeopathic preparations are regulated by FDA as drugs⁹⁰ and must have a therapeutic indication for a self-limiting, self-diagnosable condition. FDA has not reviewed any products labeled as homeopathic under the OTC Review process for drugs, because these agents are categorized as a separate entity and FDA has deferred consideration of them.⁹¹ Homeopathic products and ingredients do not go through any FDA approval process, nor are they subject to any nonprescription monograph approval. They are governed by the Homeopathic Pharmacopoeia of the United States (HPUS) and its supplements, which are produced by the Homeopathic Pharmacopoeia Convention of the United States.⁹² The same criteria under the FDCA for a determination of nonprescription or prescription status apply to homeopathic products. The regulatory framework for marketing is found in FDA’s Compliance Policy Guide (CPG), specifically, CPG 7132.15.

Labeling of homeopathic products includes the word “homeopathic” but also includes a “Drug Facts” box, which could result in confusion that the products are FDA approved. However, the ingredients are listed in terms of dilution (e.g., 1X, 6X, 2C)—a clear difference from conventional product labeling. The dosing is covered in [Chapter 52](#), along with efficacy concerns. These products must comply with display panel requirements but are exempt from expiration dating. Advertising of these products is regulated by FTC. Homeopathic drugs were not included in either the DESI or the Nonprescription Drug Review and have never been required to show safety or efficacy before marketing. However, nonprescription homeopathic drugs cannot be marketed for conditions that require a prescription. Manufacturers must register with FDA, list their products, and adhere to GMPs.⁹³

More recently, FDA is taking a closer look at homeopathic products. In 2015, a

public hearing was held evaluating FDA's regulatory framework, including labeling, safety and enforcement policies, and mechanisms and means of improving such policies going forward. The homeopathic industry has grown, safety issues have emerged, and many cases of poison exposure related to homeopathic products are reported annually by the American Association of Poison Control Centers.⁹⁴ In a 2017 draft guidance, FDA indicated an intent to reexamine its enforcement policies and apply a risk-based approach focusing on products with reported safety issues, products intended for prevention or treatment of life-threatening conditions, products for vulnerable populations, and products deemed adulterated under the FDCA.⁹⁵

Dietary Supplements

Although often offered alongside nonprescription drug products on pharmacy shelves, dietary supplements are regulated by FDA's Center for Food Safety and Applied Nutrition as foods, not drugs. Although dietary supplement claims and nonprescription drug claims have different evidence standards, they may be perceived by the consumer as indistinguishable. Dietary supplements belong to a separate category that is not tightly regulated.

More than 200 million Americans take dietary supplements, and botanical dietary supplements are used by 17.9% of U.S. adults.⁹⁶ Dietary supplements are regulated under the Dietary Supplement Health and Education Act (DSHEA) of 1994.⁹⁷ Under the DSHEA, dietary supplements are defined to include "vitamins, minerals, herb or other botanical, amino acid, a substance which increases the dietary intake of it, or a concentrate, metabolite, constituent, extract, or combination of any ingredient described above."⁹⁸

Dietary supplements are not approved by FDA but are subject to the adulteration and misbranding provisions of the FDCA and should be manufactured in accordance with GMPs. GMPs are nonbinding on manufacturers, however, and herbal product manufacturers in particular have largely ignored them because of considerable variation in the ingredients for herbal preparations.⁹⁹ A petition must be filed to market new dietary ingredients (i.e., those not already marketed before 1994), thus requiring premarket notification but not an evaluation for efficacy or safety. Enforcement of this provision has been problematic, however, with only approximately 170 notices from 1994 to 2012 despite the introduction of

thousands of new supplements to the marketplace.⁹³ FDA enforcement activities such as warning letters have recently increased against dietary supplement manufacturers making medical claims. In 2019, FDA took action against 17 companies selling supplement products claiming to treat Alzheimer disease.¹⁰⁰ Also in 2019, FDA issued 12 warning letters to companies marketing dietary supplements containing DMHA (also known as 1,5-dimethylhexylamine), used for sports performance and weight loss, and phenibut (also known as β -phenyl- γ -aminobutyric acid), used as a sleep aid.¹⁰¹

Recently, FDA has mounted new efforts to strengthen regulation of dietary supplements including new 75-day premarket notification requirements for new dietary ingredient (NDI) notification and implementation of a dietary supplement ingredient advisory list.¹⁰² The list is intended to quickly alert the public when FDA identifies ingredients that do not appear to be lawfully marketed in dietary supplements. Under the DSHEA, labels must bear the term “dietary supplement,” and each ingredient must have the quantity stated. For a proprietary blend, however, the quantities of each ingredient are not stated; only a net contents for the blend is included. Inactive ingredients must be listed in descending order of predominance. The labeling must contain a *Supplement Facts* panel identifying the dietary ingredient(s) contained in the product. When no daily recommended dose has been established, the dietary supplement may be marketed without this information. Such products also may be marketed in any combination of supplement ingredients (e.g., calcium plus magnesium).¹⁰³ Although FDA requires that manufacturers verify that every supplement they produce is safe and accurately labeled, the system essentially operates on the honor code. Under DSHEA, a dietary supplement deemed unsafe may continue to be marketed until the courts rule in FDA’s favor.¹⁰⁴

Advertising claims in all media are regulated by FTC. However, FDA is responsible for claims on product labeling. [Chapter 50](#) provides information about proper labeling of dietary supplement products.

Dietary supplement manufacturers are subject to GMPs and FDA inspection. Nevertheless, these products often have been found to be tainted with active pharmaceutical ingredients or adulterated with other ingredients, or fail to contain the purported active ingredient, or may be sold at toxic doses.¹⁰⁵ The DSHEA requires the government to bear the burden of proof to show that a dietary supplement is either adulterated or misbranded, and each case must

be tried de novo. Categories of dietary supplements that often have been found to be tainted include male enhancement supplements,¹⁰⁶ herbal products, and weight loss products. FDA's Medication Health Fraud website (<https://www.fda.gov/consumers/protecting-yourself/health-fraud-scams>) is a useful resource for information regarding tainted products sold as dietary supplements. Additionally, to improve regulation of dietary supplements, FDA has created an Office of Dietary Supplements Programs. One FDA initiative is unit-of-measure label changes from international units (IU) to metric units of measure (mcg or mg) for nonprescription vitamins A, D, and E. Also required is the listing of the absolute amounts of vitamins and minerals in metric units in addition to the percent daily value (%DV) on the label.¹⁰⁷ The Institute for Safe Medication Practices (ISMP), a nonprofit organization dedicated to development of such practices, notes that most health care practitioners remain unaware of the change, making safe transition to metric-only labeling difficult and confusing.¹⁰⁸ Chapter 50 provides a more in-depth look at dietary supplements.

Direct-to-Consumer Diagnostic Devices

Unlike nonprescription drugs, the in vitro direct-to-consumer tests marketed today are considered devices that may or may not be reviewed by FDA's Center for Devices and Radiological Health. For example, carrier screening tests, ancestry tests, and low-risk general wellness tests do not require FDA premarket review, whereas cancer predisposition tests, pharmacogenetics tests, and generic health risk tests generally require FDA clearance. Direct-to-consumer tests may be approved via a Premarket Approval (PMA) application or via the 510(k) route, or not at all, depending upon the risk classification.¹⁰⁹ A company with 510(k) clearance for a prescription device will need to submit a new 510(k) form to market the product for nonprescription use. Data will be required to show that consumers can use the device and interpret the results without the assistance of a health care professional.¹¹⁰ FDA has created a database of nonprescription in vitro device tests it regulates.¹¹¹ Point-of-care testing can be self-initiated, as when the patient is responding to symptoms, or prescriber-initiated, as when a sample is taken in the home environment or clinic and returned to be assayed in a laboratory.

A majority of direct-to-consumer tests sold today are genetic test kits (e.g., 23andMe). Others measure levels of drugs of abuse or toxins in urine, or levels

and types of bacteria. Considerable consumer interest in kits for human immunodeficiency virus (HIV) testing and for cholesterol screening and monitoring continues to grow. All point-of-care laboratory testing in pharmacies is subject to regulation by the Centers for Medicare & Medicaid Services as part of the Clinical Laboratory Improvement Amendments (CLIA) program. However, most point-of-care tests conducted in community pharmacies or at health screenings are considered CLIA waived. To obtain a CLIA waiver, the pharmacy must first obtain a CLIA certificate and then apply for laboratory status at the state level, usually through the state health department.¹⁰⁰ Each state has its own CLIA program and may impose additional requirements or restrictions. Pharmacies with CLIA waivers are still subject to inspection to ensure compliance and also must comply with standards set forth in Occupational Safety and Health Administration (OSHA) universal precautions to reduce risk of exposure to blood-borne pathogens.

Currently, approximately 18% of community pharmacies have a CLIA waiver and can perform CLIA-waived tests such as determination of the international normalized ratio (INR), blood glucose, glycosylated hemoglobin (HbA_{1c}), and lipid profile.¹¹² With the upsurge in pharmacy-based disease state management programs and health screening-related collaborative practice agreements, the number of pharmacies with CLIA waiver status is likely to increase in the future.

Nonprescription Product Liability

Most legal cases involving nonprescription drugs are product liability cases, brought against manufacturers, not pharmacies or pharmacists. Although not as common as claims against prescription drugs, incidents involving nonprescription drugs have been the subject of civil litigation. Claims are brought for breach of the Implied Warranty of Fitness¹¹³ and for breach of the Implied Warranty of Merchantability.¹¹⁴ Recovery under these legal theories is generally limited to issues related to sale of a product, rather than performance of a service in which a defective product may be involved only incidentally. When the service being performed is a professional service, such as with a pharmacist recommendation for a defective nonprescription product, the courts exhibit a reluctance to impose strict liability without fault. However, the pharmacist may still be liable for negligence and/or intentional misconduct as appropriate to the facts of the case.¹¹⁵ In litigation in which a

pharmacist sold the patient camphorated oil instead of castor oil, with subsequent harm to the patient, the court held the pharmacist negligent.¹¹⁶

For the nonprescription drug plaintiff, the first evidentiary hurdle is proof of purchase, which can result in a summary judgment on this threshold issue. The injured party will need to furnish a receipt or other evidence of proof of purchase. Causation is another issue, in that a purchased nonprescription product may sit in the medicine cabinet for months before actual use. It is difficult to prove, with mere plaintiff testimony, proximity in time between use of the product and injury. However, unlike the case with prescription drugs, in which the learned intermediary (the prescriber) is a defense for manufacturers, for nonprescription drug products, manufacturer warnings must go directly to the consumer. In *Yugler v. Pharmacia & Upjohn Co.*, the court denied application of the learned intermediary doctrine, even when the provider had initially prescribed prescription Motrin and the patient obtained refills over the counter.¹¹⁷

Liability for Advice on Nonprescription Drugs

Pharmacists can be sued for malpractice and negligence for inaccurate advice (with liability requiring affirmative misrepresentations) regarding nonprescription drugs that harm the patient. A recommendation for use of a nonprescription product not in accordance with the labeling may increase the risk for liability if the patient is harmed. Additionally, in a case in which a pharmacist recommended a nonprescription product in place of the prescribed one, and the patient was harmed, the court denied the pharmacy's motion for summary judgment that the patient was "contributory negligent" in ignoring the label directions.¹¹⁸

A recent high-profile case centering on pharmacists' advice for nonprescription products is *Whiting v. Rite Aid Pharmacy*,¹¹⁹ wherein the patient's estate sued the pharmacist for a recommendation that the patient could safely take phenylpropanolamine and Sudafed. The plaintiff contended that she informed the pharmacist of the patient's prostate problems. The pharmacist denied that the conversation ever occurred. The plaintiff asserted that the use of the drug exacerbated the patient's prostate condition, resulting in the need for several surgeries and, ultimately, his death several years later from an unrelated illness. The pharmacy contended that learned intermediary doctrine protects the pharmacist from such liability and that the pharmacist's

duty of care does not require giving adequate advice about nonprescription drugs. Falling under the learned intermediary doctrine is a defense of tort lawsuits stating that the duty to warn of the dangers of a nonprescription product is that of the manufacturer. The court ruled that the learned intermediary doctrine applies only to prescription drugs. Additionally, however, the court was clear with respect to the duty of care for pharmacists¹¹⁹:

Pharmacists in Utah clearly have duties regarding nonprescription drugs. If a pharmacist answers a customer's question and offers advice about nonprescription drugs, the pharmacist must advise and act in a non-negligent manner consistent with a reasonably prudent pharmacist's response to a customer's question about the safety of a nonprescription drug.

Ingredients in nonprescription drug products change often, and pharmacists should be certain of a product's ingredients and contraindications before recommending it. The Drug Facts labeling of the product should form a basis for any patient consultation and advice on nonprescription drug products. Counseling for patient education should be routinely and briefly documented.¹²⁰ As nonprescription marketing of medications becomes more prevalent in the United States, litigation against manufacturers of nonprescription drug products will similarly increase.

Liability Associated With Nonprescription Drugs

Strict liability could apply to pharmacists for failure to effect timely removal of a recalled or expired product from the shelves when a patient is harmed. The courts have generally ruled that no liability accrues to the pharmacist for defective medications sold in prepackaged containers. However, if a pharmacy repackages the drug with its own label, it may be held liable.¹²¹ The label of the repackaged drug should contain the same amount of information as on the original label.¹⁰ In *Patrick v. Carrier Stevens Co.*,¹²² the plaintiff prevailed when he purchased a flea repellant warranted by the pharmacist as safe for his pet even if ingested, but which then subsequently harmed his other animals.

Manufacturers are subject to strict liability for harm caused by a "product in a defective condition unreasonably dangerous to the user or consumer."¹²³ Class action lawsuits for defective nonprescription products continue to be initiated, especially when the company delayed in warning consumers of ADRs. Notable

examples of adverse events involving nonprescription drugs leading to class action lawsuits are severe, potentially fatal hypersensitivity allergic reactions from nonprescription acne products; bone fractures and hypomagnesemia from proton pump inhibitors; and Stevens-Johnson syndrome and toxic epidermal necrolysis from ibuprofen.¹²⁴⁻¹²⁶

The Future: Innovative Approaches for Nonprescription Drug Products

Innovation under the OTC Monograph system is slow, cumbersome, and difficult, in that changing a monograph requires utilization of the rule-making process (Advance Notice of Proposed Rulemaking, Tentative Final Monograph or Final Monograph). FDA recognizes that at times both the OTC Monograph and the NDA processes are cumbersome, and in an effort to reduce health care costs, the agency has taken several steps toward making more medications available without a prescription, including those for some chronic conditions. In 2018, FDA issued a guidance document that detailed two innovative approaches to demonstrate safety and efficacy for products when the Drug Facts labeling (DFL) alone is not sufficient to ensure that the product can be used in a nonprescription setting.¹²⁷ The innovative approaches involve (1) the development of labeling in addition to the DFL and (2) the implementation of additional requirements so that consumers appropriately self-select and use the product.

On March 27, 2020, the U.S. Congress passed the Coronavirus Aid, Relief and Economic Security Act (CARES Act).¹²⁸ This statute includes landmark legislation to reform the nonprescription drug review monograph system by granting FDA transformative new authorities to modernize the nonprescription drug development and review process. Under this act, new processes to update existing monographs replace the multilayered rule-making process that posed inherent difficulties in updating product labels with new safety information and had caused a backlog of nonprescription drug monographs.

In addition to an increase in FDA staff and funding, the statute includes the following provisions:

- Establishment of a centralized database of information and labeling requirements
- Establishment of timelines for FDA reviews together with user fees for nonprescription drug manufacturers and those utilizing the administrative review process
- Creation of an administrative review process (via administrative orders) that replaces the monograph system
- Categorization of currently marketed nonprescription drugs that are GRASE (previously referred to as *Category I*) as either those that can be marketed over the counter or as new drugs that require submission of an NDA
- Creation of an 18-month exclusivity period for new nonprescription drugs
- Authorization for FDA to issue administrative orders on its own initiative when a nonprescription product poses an imminent hazard to public health
- Sunsetting of the Sunscreen Innovation Act¹²⁹ and its alternative processes for review of this class of products
- Exclusion of homeopathic drugs from the nonprescription drug review process

The new process was intended to facilitate the review of new ingredients and to clarify the legal and regulatory status of tentative final monograph products. Drugs that were classified as Category III or Category I in an Advance Notice of Proposed Rulemaking will be permitted to remain on the market without approved NDAs until and unless FDA issues a final order that they are not GRASE. Category II drugs must be removed from the market within 180 days of passage of the act. New drugs (those not considered GRASE) and nonprescription drugs that are not in the other mentioned categories are subject to the NDA requirement. Administrative orders have replaced the notice-and-comment rulemaking process and can be of three types: (1) FDA-initiated, (2) expedited (e.g., imminent hazard), and (3) industry-initiated (i.e., based on submissions by sponsors seeking approval of new active ingredients or other changes such as new dosage forms). Minor changes for drugs can be implemented without Administrative Orders and in some cases by conducting studies and submitting data.¹³⁰

These changes reflect many years of work aimed at nonprescription drug reform. On the negative side, some products will be removed from the market

or will be subject to enforcement action. On the positive side, the new regulatory framework is easier and faster to use, and it is expected to result in the marketing of innovative nonprescription products with new ingredients, dosage forms (e.g., dissolvable films), and combination drugs.

Key Points

- Over the past 100-plus years, regulatory transition of nonprescription medications from patent medicines to scientifically based therapies have occurred.
- Nonprescription medications are vital to appropriate selfcare and one of the least costly components of the U.S. health care system.
- Regulation of nonprescription medications is important to protect the public but should not place limits on achieving an optimal level of personal health.
- Existing overregulation of nonprescription medications prevents patients from gaining control over their health care, increases patient costs, and requires unnecessary use of health care resources to obtain some prescriptions.
- The past few decades have seen a large number of prescription-to-nonprescription switches, and today's consumers are taking greater responsibility for their own health care.
- An essential element of collaborative clinical practice for health care professionals is a full understanding of the regulatory and legal aspects of how nonprescription products are manufactured, labeled, and marketed.

Chapter 5: Headache

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Headache is an important cause of pain and disability worldwide. The prevalence of migraine headache is 1.04 billion; for tension-type headache, the rate is 1.89 billion.¹ Tension headache is much more common, but migraine is more severe. Migraine is the second leading cause of disability globally.¹ Worldwide, 50% of the population has suffered from headache within the previous year, and among persons afflicted with headache, 30% had migraine.² Headaches caused by sinus congestion and those resulting from the overuse of analgesics also are common.

Headaches generally are classified as primary or secondary. *Primary* headaches (approximately 90% of headaches) are not associated with an underlying illness. Examples are episodic and chronic tension-type headaches, migraine headache with and without aura (sensory disturbances), and cluster headaches. *Secondary* headaches are symptomatic of an underlying condition, such as head trauma, stroke, substance abuse or withdrawal, bacterial and viral diseases, and disorders of craniofacial structures. Medication overuse headaches are considered a complication of the underlying headache disorder and are related to a withdrawal effect of medications.³ Cluster headaches and secondary headaches are not discussed in this chapter because they are not amenable to self-care management.

Tension-type headaches, also called stress headaches, can be episodic or chronic. *Chronic* headaches occur 15 or more days per month for at least 3 months, whereas episodic tension-type headaches occur less than 15 days per month.³ *Episodic* tension-type headaches are further classified as frequent episodic if at least 10 episodes of headache occur on 1–14 days per month.³ The usual onset of tension-type headache is during the teenage years; women are affected more commonly than men, in a ratio of 3:2.² Tension-type headache is generally less severe than migraine, but it may occur more frequently, leading to substantial disability.⁴

Two primary types of migraine headache are recognized: with and without aura. Migraine of either type is characterized by the presence of at least two of the following criteria: moderate to severe head pain, unilateral pain, pulsating quality of pain, and aggravation of pain by routine physical activity. In addition,

the episode must be accompanied by either nausea/vomiting or photophobia/phonophobia.⁵ Migraine with aura further includes neurologic signs and symptoms that precede or coincide with onset of the head pain and subsequently resolve fully. The neurologic manifestations may be visual, sensory, speech, language, or motor. Aura should be considered in patients with or without a headache if they have at least one neurologic sign or symptom that develops slowly during a period of at least 5 minutes, lasts for 5–60 minutes, and resolves fully. Both types of migraine may also include a prodrome or postdrome of symptoms and signs such as hyperactivity, hypoactivity, depression, food cravings, yawning, fatigue, and neck pain or stiffness. A *prodrome* refers to one or more such signs and symptoms occurring before clinical onset of the migraine; a *postdrome* is one or more manifestations emerging after the migraine episode.³

The prevalence and impact of migraine and severe headache of other etiology in the United States have been evaluated in several national surveys.⁶ Researchers found that nearly 1 of every 6 Americans reported suffering from severe headache within a 3-month period (15.3% overall [95% CI 14.75–15.85]). The prevalence was twice as high in females as in males (20.7% versus 9.7%). Among ethnic groups, the rate was highest in American Indian or Alaska Natives at 18.4% and lowest in Asians at 11.3%. The estimated rates for whites, blacks, and Hispanics were 16.6%, 15.4%, and 14.5%, respectively. This condition is more common in younger adults without other health conditions. Headache is the fifth most common reason for emergency department visits, accounting for 3% of all such visits.⁶

Patients with a preexisting headache disorder who experience headache on 15 or more days per month and who regularly use headache medications for longer than 3 months may be suffering from medication overuse headaches. This problem is clinically important: Estimated frequency of medication overuse ranges from 11% to 63%.⁷ The available research methods are limited in their ability to clarify the effect of the medication overuse as a factor distinct from underlying headache severity.⁷

Sinus headache is frequently reported in patients with acute sinusitis. These patients also experience other sinus symptoms such as facial tenderness and pain, nasal congestion, and nasal discharge. Although rhinosinusitis leads to pain, it does not usually manifest as frontal head pain. If the patient is experiencing head pain while congested, it also may be caused by migraine or

tension-type headache.⁸

The economic impact of headache is substantial. Researchers have estimated the burden of the disease using the measure of years of life lived with disability (YLDs). Migraine was found to have caused 45 million YLDs and tension-type caused 7 million YLDs worldwide in 2016.¹ Most studies looking at the economic burden of headache have focused on migraine headache. Annual direct medical costs of migraine average \$13,045 per patient.⁹ The combination of direct costs for medical services and indirect costs from lost productivity and wages adds up to more than \$14 billion annually for U.S. employers.⁹

This chapter focuses on the most common types of headaches that are amenable to self-treatment: tension-type, diagnosed migraine, and sinus headaches. Medication overuse headache also is discussed, in keeping with the pharmacist's role in preventing this type of headache through counseling; however, this type of headache requires a medical referral if it occurs. Nonprescription analgesics are useful for treating headache, either in monotherapy regimens or as adjuncts to nonpharmacologic or prescription therapy. An important category of these medications is the class of nonsteroidal anti-inflammatory drugs (NSAIDs), which include aspirin and other salicylates as well as ibuprofen and naproxen. Many headache sufferers self-treat with nonprescription remedies, rather than seeking medical attention. As much as two thirds of nonprescription analgesic use may be for headache.¹⁰ Researchers found that 24% of patients chronically overused medication and that only 14.5% had ever been advised by a health care provider to limit their intake of acute headache remedies.¹⁰ Careful evaluation, counseling, and referral for prescription-only treatments have great potential to improve quality of life for many affected persons.

Pathophysiology of Headache

Tension-type headaches often arise in response to stress, anxiety, depression, emotional conflicts, or other stimuli. Myofascial tissues in the pericranial area contain nociceptors that play a role in the pathophysiology of tension-type headaches.¹¹ The episodic tension-type headache subtype is thought to result in pain sensed by the peripheral nervous system, whereas the chronic subtype is thought to result from stimuli to the central nervous system.³ A genetic component is likely in predisposition (or resistance) to development of tension-

type headaches. Furthermore, tension-type and migraine headaches appear to share pathophysiologic features, making them more similar than distinct.¹²

Migraine headache is a neurobiologic disorder. According to current evidence-based theory, migraine-associated pathophysiologic changes originate in the central nervous system, rather than primarily in the vascular system. Pain pathways are stimulated and messenger molecules are involved, including nitric oxide, serotonin, and calcitonin gene-related peptide. The trigeminovascular system also plays a role.³ Stress, fatigue, irregular sleep patterns, fasting or missing a meal, vasoactive substances in food, caffeine, alcohol, changes in female hormones, changes in barometric pressure and altitude, bright lights, odor, neck pain, exercise, and smoking all may trigger migraine.⁵ Medications (e.g., reserpine, nitrates, oral contraceptives, postmenopausal hormones) also have been identified as triggers. The pathophysiology of migraine with aura involves neuronal depolarization that spreads slowly across the cerebral cortex during the aura phase.¹³ Magnesium deficiency may contribute to this state.¹⁴ During the headache phase, stimulation (by an axon reflex) of trigeminal sensory fibers in the large cerebral and dural vessels causes neuropeptide release with concomitant neurogenic inflammation, vasodilation, and activation of platelets and mast cells.¹³

As mentioned previously, changes in female hormone levels may cause migraines. Migraines related to the menstrual cycle occur in less than 10% of women and generally are not associated with aura.³ Attacks during menstruation may have a longer duration and feature more severe nausea. With menstrual migraine, pathophysiologic changes are mediated by estrogen withdrawal.¹⁵ *Medication overuse headache* results from excessive use of analgesics, which may cause a change from episodic headaches to chronic headaches. This type of headache is distinct from that occurring as an adverse effect of certain medications such as nitrates and phosphodiesterase type-5 inhibitors. Some patients who suffer from migraine or tension-type headaches receive limited relief from analgesics and over time may increase their use of one or more such drugs, which can lead to development of medication overuse headaches. These headaches usually are associated with frequent medication use (more than twice weekly) for 3 months or longer. Onset of the headache occurs within hours of stopping the agent, and readministration of the agent provides relief. Medication overuse headache should be suspected if the frequency of headaches is 15 days per month or greater in patients taking analgesics including acetaminophen, aspirin, ibuprofen, naproxen, or

prescription NSAIDs for a duration of 3 months. Headache frequency of 10 days per month after taking triptans, opioids, ergots, or combination analgesics for 3 months should be evaluated.¹⁶ Caffeine, butalbital, and ergotamine also may cause medication overuse headache. *Sinus headache* occurs when infection or blockage of the paranasal sinuses causes inflammation or distention of the sensitive sinus walls (see [Chapter 11](#)). Sinus congestion may be caused by viral or bacterial infection, or by allergic rhinitis. Pathophysiologic mechanisms at work during migraine headache can result in prominent sinus congestion, leading to confusion about which problem is the cause and which is the effect.

Clinical Presentation of Headache

Headaches can be differentiated by their signs and symptoms; the major defining characteristics are listed in [Table 5–1](#). It is important to distinguish primary from secondary headaches because a headache can indicate a life-threatening condition. Exclusions to self-care, shown in [Figure 5–1](#), are important because of the seriousness of certain disorders that manifest with headache. The severity of pain associated with tension-type headaches is highly variable. Some headaches are so mild they do not require treatment, whereas others are sufficiently severe to be disabling. Episodic tension-type headaches may last a few hours, but duration up to several days has been described. Chronic tension-type headaches often are more severe and frequently last for several days. The pain initially feels like pressure or tightening on both sides of the head and subsequently may spread to feel like a band around the head.^{2,3}

Table 5–1 Characteristics of Tension-Type, Migraine, and Sinus Headaches			
Feature	Tension-Type Headache	Migraine Headache	Sinus Headache
Location	Bilateral	Usually unilateral	Face, forehead, or periorbital area
Nature	Diffuse ache, tightening, pressing, constricting	Throbbing, pulsating	Pressure behind eyes or face, dull and bilateral pain
Intensity	Mild–moderate	Moderate–severe	Mild–severe

Feature	Tension-Type Headache	Migraine Headache	Sinus Headache
Onset	Gradual	Sudden	Simultaneous with sinus symptoms
Duration	30 minutes to 7 days	4–72 hours	Days (resolves with sinus symptoms)
Aggravating factors	Stress, anxiety	Physical activity, light, sound	Nasal congestion
Non-headache symptoms	Scalp tenderness, neck pain and muscle tension	Nausea, vomiting, aura	Nasal congestion nasal discharge

Source: References 3 and 16.

Migraine headaches are classified as migraine with or without aura. *Aura* manifests as a series of neurologic signs and symptoms: ocular perceptions of shimmering or flashing areas or blind spots, visual and auditory hallucinations, muscle weakness that usually is one-sided, and difficulty speaking (occurring rarely). These symptoms may last up to 30 minutes, and the throbbing headache pain that follows may last from several hours to 3 days. Of note, however, aura is not always followed by a migraine headache. Migraines without aura begin immediately with throbbing headache pain. Both forms of migraine often are associated with nausea, vomiting, photophobia, phonophobia, sinus symptoms, tinnitus, light-headedness, vertigo, and irritability and are aggravated by routine physical activity.⁵ Premonitory (prodrome) signs and symptoms in migraine can be neuropsychiatric (e.g., anxiety, irritability, yawning, emotional distress, insomnia), sensory (e.g., phonophobia, photophobia, focusing difficulties, speech difficulties), digestive (e.g., food craving, nausea, vomiting, diarrhea, constipation), or general (e.g., asthenia, fatigue, fluid retention, urinary frequency). Premonitory signs and symptoms can be a feature of migraine headaches with and those without aura.

Medication overuse headache occurs as a rebound phenomenon after repeated and excessive use of the implicated drug in a patient with an

episodic headache disorder. Continued overuse causes headache symptomatology to shift from the baseline headache type to a nearly continuous headache, particularly noticeable on awakening. Additional symptoms may include difficulty concentrating, lethargy, irritability, and nausea.

Sinus headache usually is localized to facial areas over the sinuses and is difficult to differentiate from migraine without aura. The pain of a sinus headache typically is described as dull and pressure-like. Stooping or blowing the nose often intensifies the pain, but the headache is not accompanied by nausea, vomiting, or visual disturbances. Persistent sinus pain and/or discharge suggests possible infection and warrants referral for medical evaluation.

Algorithm: Headache

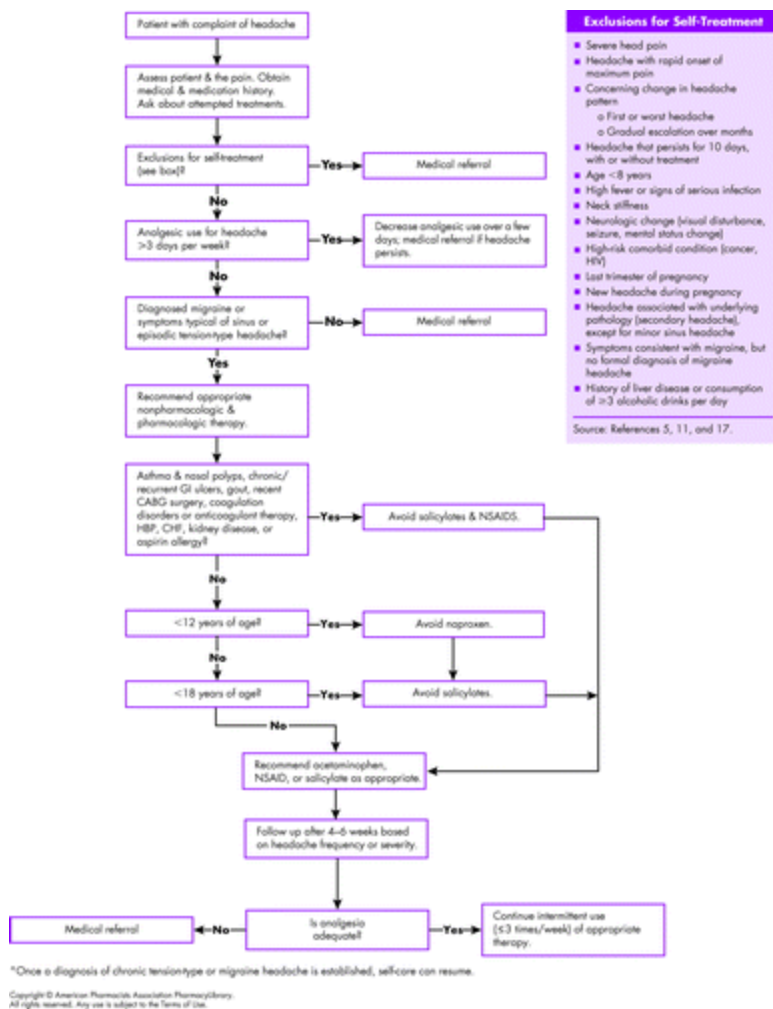


Figure 5–1 Self-care for headache. Key: CABG = Coronary artery bypass graft; CHF = congestive heart failure; GI = gastrointestinal; HBP = high blood pressure; HIV = human immunodeficiency virus; NSAID = nonsteroidal anti-inflammatory drug.

Treatment of Headache

Treatment Goals

The goals of treating headache are (1) to reduce the severity and alleviate acute pain, (2) to restore normal functioning, (3) to prevent relapse, and (4) to minimize adverse effects. For chronic headache, an additional goal is to reduce the frequency of headaches.

General Treatment Approach

Most patients with episodic headaches obtain an adequate response to self-treatment with nonpharmacologic interventions, nonprescription medications, or both. However, some patients with episodic headaches and most with chronic headaches are candidates for prescription treatments.

Episodic tension-type headaches often respond well to nonprescription analgesics, including acetaminophen and NSAIDs such as salicylates, especially when taken at the onset of the headache.¹⁶ If nonprescription analgesics are used to treat chronic headache, frequency of use should be limited to less than 3 days per week or 14 days per month, to prevent medication overuse headache.¹⁷ Patients with chronic tension-type headaches may benefit from physical therapy and relaxation exercises in addition to nonprescription or prescription medications. [Figure 5–1](#) outlines selfcare for headaches and lists exclusions for self-treatment.^{5,11,17–19}

A medical diagnosis of migraine is required before self-treatment can be recommended. First-line pharmaceutical agents for relief of migraine headache include triptans, NSAIDs, and combinations of a triptan with acetaminophen or an NSAID.¹⁶ Taking an NSAID, such as a salicylate, at the onset of symptoms can abort mild or moderate migraine headache. Analgesics work best in the early stages of a migraine. Patients with migraine who can predict the occurrence of the headache (e.g., during menstruation) should take an analgesic before occurrence of the event known to trigger the headache, as well as throughout the duration of the event. For patients with coexisting tension and migraine headaches, treatment of the initiating headache type can abort the mixed headache. Antiemetic treatment also is indicated.¹⁶ Prophylactic therapy for migraine includes various regimens of beta blockers, tricyclic antidepressants, calcium channel blockers, divalproex, topiramate, or gabapentin.⁵

When medication overuse headache is suspected, use of the offending agent(s) should be stopped immediately for a period of at least 1 month. Discontinuation of the medication should be done with medical supervision because prescription therapies may be needed to combat the increased headaches that temporarily ensue during the days to weeks of the withdrawal period. Additionally, medication may be needed to treat the baseline headache disorder that caused the initial overuse of the headache medications.¹⁶

Sinus headaches respond well to oral and nasal decongestants (e.g., pseudoephedrine, oxymetazoline), which reduce congestion by causing vasoconstriction in the nasal passages (see [Chapter 11](#)). Concomitant use of decongestants and nonprescription analgesics can relieve sinus headache pain. Chronic congestion and sinus infections may be a sign of structural abnormalities and indicate the need for an appropriate medical referral.

Nonpharmacologic Therapy

Patient education is an important component of self-care management of headache. Information about the underlying diagnosis, safe medication use, and lifestyle modification should be included to optimize the self-treatment regimen. Keeping a headache diary for a minimum of 8 weeks to record frequency, duration, related symptoms, precipitating factors, medications used for relief, and menstruation schedule may improve diagnostic accuracy and medication management.¹⁶ Acupuncture studies have yielded some evidence supporting a role for this modality in reducing the frequency and intensity of headache. Manual therapy offered by osteopathic physicians, chiropractors, and massage therapists has been shown to result in short-term improvement in persons with headache.²⁰ Adjunctive therapy for tension-type headache includes stress management and physical therapy.⁵

General treatment measures for migraine include maintaining a regular schedule for sleeping, eating, and exercise; stress management; biofeedback; and cognitive therapy. Some patients obtain relief from the pain of acute migraine attacks by resting in a quiet dark room and applying ice or cold packs combined with pressure to the forehead or temple areas. Nutritional strategies are intended to prevent migraine and are based on (1) dietary restriction of foods that contain trigger substances, (2) avoidance of hunger and low blood glucose (a trigger of migraine), and (3) magnesium supplementation.^{14,21} Advocates of nutritional therapy recommend avoiding known food allergens and foods with vasoactive substances, such as nitrites (found in cured meats), tyramine (found in red wine and aged cheese), phenylalanine (found in the artificial sweetener aspartame), monosodium glutamate (often found in Asian food), caffeine, and theobromines (found in chocolate).²¹

Pharmacologic Therapy

Available nonprescription analgesics for the management of headache include

acetaminophen and NSAIDs such as ibuprofen and naproxen and especially salicylates (aspirin and magnesium salicylate). Selection of an analgesic should be based on a careful review of the patient's medical and medication histories. Medical management of nausea accompanying migraine headache also may be indicated to improve symptomatic relief and to facilitate medication delivery by the oral route.

Acetaminophen

Acetaminophen is an effective analgesic and antipyretic. According to long-standing hypothesis, acetaminophen produces analgesia through central inhibition of prostaglandin synthesis. A broader view, however, is that its mechanism of action may be more complex, involving aspects that are not yet fully understood. Other suggested mechanisms, for example, include descending serotonergic pathway activation and endocannabinoid reuptake inhibition.²²

Acetaminophen is absorbed rapidly from the gastrointestinal (GI) tract and extensively metabolized in the liver to inactive glucuronic and sulfuric acid conjugates. Acetaminophen also is metabolized by the cytochrome P450 enzyme system to a hepatotoxic intermediate metabolite that is detoxified by glutathione. When given by suppository, acetaminophen has a rectal bioavailability of approximately 50%–60% of that achieved with oral administration. Onset of analgesic activity of acetaminophen occurs approximately 30 minutes after oral administration. Duration of activity is approximately 4 hours and is increased to 6–8 hours with an extended-release formulation.

U.S. Food and Drug Administration (FDA)-approved uses for nonprescription acetaminophen include reducing fever and relieving mild to moderate pain. It is effective in relieving mild to moderate pain of nonvisceral origin (i.e., pain that is not organ-related). Randomized, double-blind studies have documented the effectiveness of acetaminophen 1000 mg over placebo in patients with migraine and tension-type headache.²³

Recommended child and adult dosages of acetaminophen are provided in [Tables 5–2](#) and [5–3](#).²⁴ [Table 5–4](#) lists selected trade-name products.

Acetaminophen is available for administration in various oral and rectal dosage forms.

Table 5–2 FDA-Approved Dosages for Nonprescription Analgesics in Children Younger Than 12 Years

Dosage Basics	Ibuprofen (mg)	Acetaminophen (mg)	
Weight-based dosing	5–10 mg/kg	10–15 mg/kg	
Dosing schedule	Every 6–8 hours as needed	Every 4–6 hours as needed	
Maximum daily dose	300 mg per dose up to 4 doses, or 40 mg/kg/day; not to exceed 1200 mg total daily dose	480 mg per dose up to 5 doses, or 75 mg/kg/day; not to exceed 2400 mg total daily dose	
Age Group	Weight (lb)		
6–11 months	12–17	50	80 mg ^a
12–23 months	18–23	75	120 mg ^a
2–3 years	24–35	100	160
4–5 years	36–47	150	240
6–8 years	48–59	200	320
9–10 years	60–71	250	400
11 years	72–95	300	480

^a Labeling recommends referral to primary care provider before use.

Key: FDA = U.S. Food and Drug Administration.

Source: [Reference 24](#).

Table 5–3 Recommended Dosages of Nonprescription Analgesics for Adults and Children 12 Years and Older

Agent	Dosage Forms	Usual Adult Dosage (maximum daily dosage)
Acetaminophen	Immediate-release, extended-release, effervescent, dispersible, and chewable tablets; capsules; liquid; suppositories; powder packet	325–1000 mg every 4–6 hours as needed for immediate-release products (3000 mg, <i>or</i> 4000 mg ^a) 650–1300 mg every 8 hours as needed for extended-release products (3000 mg, <i>or</i> 4000 mg ^a)
Ibuprofen	Immediate-release and chewable tablets; capsules; suspension	200–400 mg every 4–6 hours as needed (1200 mg)
Naproxen sodium	Immediate-release and delayed-release tablets, capsules	220 mg every 8–12 hours as needed (660 mg) <i>For initial dose: 2 tablets within the first hour</i>
Aspirin	Immediate-release, buffered, enteric-coated, film-coated, effervescent, and chewable tablets; suppositories	325–1000 mg every 4–6 hours as needed (4000 mg)
Magnesium salicylate	Tablets	1160 mg every 6 hours as needed (4640 mg)

^a Maximum daily dose of regular-strength (325 mg) products: 3250 mg, *or* 4000 mg with supervision of HCP; extra-strength (500 mg) products: 3000 mg, *or* 4000 mg with supervision of HCP; extended-release (650 mg) products: 3900 mg.

Key: FDA = U.S. Food and Drug Administration; HCP = health care provider.

Source: [Reference 24](#).

Table 5–4 Selected Single-Entity Nonprescription Acetaminophen Products

Trade Name	Acetaminophen Content
Pediatric Formulations	

Trade Name	Acetaminophen Content
FeverAll Infants' Suppository	80 mg
FeverAll Children's Suppository	120 mg
FeverAll Jr. Strength Suppository	325 mg
Children's Tylenol Oral Suspension	160 mg/5 mL
Adult Formulations	
Tylenol Regular Strength Tablets	325 mg
Tylenol Extra Strength caplet	500 mg
Tylenol 8 HR Arthritis Pain Extended-Release caplet	650 mg
Tylenol 8 HR Muscle Aches & Pain Extended-Release tablet	650 mg
Tylenol Cold + Sore Throat COOL BURST Liquid	500 mg/15 mL

Source: [Reference 24](#).

Acetaminophen oral capsules contain tasteless granules that can be added to a spoon containing a small amount of cold beverage (hot beverages result in a bitter taste) or soft food. Capsule contents should not be combined with larger quantities of liquid because a significant proportion of the granules may adhere to the container surface.

Acetaminophen is potentially hepatotoxic in doses exceeding 4 g daily, especially with chronic use. Patients should be cautioned against exceeding the dose limit. More conservative dosing (i.e., ≤ 2 g daily) or complete avoidance may be warranted in patients at increased risk for acetaminophen-induced hepatotoxicity, specifically those with diagnosed liver disease, concurrent use of other potentially hepatotoxic drugs, poor nutritional intake, or consumption of three or more alcoholic drinks per day.²⁵ One alcoholic drink is defined as 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of 80 proof liquor.

FDA requires manufacturers to include a boxed warning on acetaminophen

products that addresses its potential to cause hepatotoxicity. The basic language of the warning is as follows:

Liver warning: This product contains acetaminophen. Severe liver damage may occur if

- an adult takes more than 4000 mg of acetaminophen in 24 hours
- a child takes more than 5 doses in 24 hours, which is the maximum daily amount
- the product is taken with other drugs containing acetaminophen
- an adult has three or more alcoholic drinks every day while using this product

The warning varies depending on whether the product is labeled for use in children and/or adults. In order to decrease acetaminophen-induced hepatic injury, FDA limited the acetaminophen content of prescription-only combination opioid analgesics to 325 mg per dosage unit.^{26,27} FDA also has recommended that manufacturers of nonprescription products lower the maximum daily dose from 4000 mg to 3250 mg per day and to limit pediatric oral dosage forms to a single strength of 160 mg.^{28,29} McNeil followed this recommendation by listing a maximum daily dose of 3250 mg for regular-release products and 3000 mg for extra-strength products (dosing interval of every 6 hours as opposed to every 4–6 hours). However, 650-mg extended-release products have a maximum daily dose listed as 3900 mg. Errors in dosing occur with the 650-mg extended-release formulation because patients do not understand that they need to wait 8 hours between doses.²⁶

Acetaminophen poisoning is a major reason for contacting poison control centers and constitutes the leading cause of acute liver failure in the United States.³⁰ Unintended chronic overdose accounts for approximately one half of the cases of acetaminophen-induced acute liver failure. Researchers have documented that significant knowledge gaps lead to incorrect dosing.³¹ Contributing factors include repeated dosing in excess of package labeling, use of more than one product containing acetaminophen, and concurrent alcohol ingestion. It is estimated that in 30% of emergency department visits for acetaminophen poisoning, the overdose was unintentional.³¹

Acetaminophen toxicity evolves in four stages. Stage I includes signs and symptoms of nausea, vomiting, drowsiness, confusion, and abdominal pain, but such early manifestations may be absent or delayed, belying the potential

severity of the exposure. Stage II is characterized by emergence of the first symptoms of hepatotoxicity and begins 24–48 hours after acute ingestion of acetaminophen. Stage II signs and symptoms include increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT), increased bilirubin with jaundice, prolonged prothrombin time, and obtundation. Stage III develops after 3 or 4 days and progresses to liver failure in the absence of treatment. Signs and symptoms at this stage may include metabolic acidosis, encephalopathy, cerebral edema, and renal failure. GI symptoms may also be present during this stage. Stage IV begins 4 days after ingestion and can last for several weeks. During this stage, in a majority of cases, hepatic damage is reversible over a period of weeks or months, but more severe cases may require liver transplantation or result in fatal hepatic necrosis.³²

Because of the potential seriousness of acetaminophen overdose, all cases should be referred to a poison control center or hospital emergency department. Supportive care is provided, along with activated charcoal to reduce acetaminophen absorption in patients who present for treatment within 1 hour after ingestion. When acetaminophen serum levels, with consideration of time since ingestion, exceed those known to cause hepatic injury, prompt administration of acetylcysteine is warranted to supplement glutathione, which is essential for deactivation of a toxic intermediate metabolite of acetaminophen. Acetylcysteine's effectiveness decreases if it is administered more than 8 hours after acute ingestion. Asymptomatic elevations in ALT have been reported in otherwise healthy persons taking acetaminophen 4 g daily. In a prospective study, 39% of patients experienced ALT elevations to greater than three times the upper limit of normal. These elevations generally appeared in the first week of use, with some resolution occurring despite continued dosing. The clinical significance of this observation is uncertain.³³

Patients with glucose-6-phosphate dehydrogenase deficiency, a hereditary disease that causes premature breakdown of red blood cells, are at increased risk for adverse reactions to acetaminophen. It is unclear whether regular doses of acetaminophen will cause toxicity in patients with such deficiency; however, case reports of hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency who took an excessive amount of acetaminophen have been recorded.³⁴ In patients with hypersensitivity to acetaminophen, the drug is contraindicated for future use.

Rare but serious cutaneous adverse reactions (SCARs) have been found to be associated with use of acetaminophen as well as other analgesics including NSAIDs. Skin reactions may occur in either new or current users of the drug and have the potential to progress to a life-threatening rash, as in Stevens-Johnson syndrome and toxic epidermal necrolysis. Although these events are very rare, it is important to be aware of the possibility and to refer patients as appropriate for further evaluation.³⁵ FDA recommends that the following language appear in the Warnings section of the Drug Facts Label for all single-ingredient and combination-ingredient acetaminophen products:

Allergy alert: Acetaminophen may cause severe skin reactions. Symptoms may include

- skin reddening
- blisters
- rash

If a skin rash occurs, stop use and seek medical help right away.³⁵

Clinically important drug interactions for acetaminophen are listed in [Table 5–5](#). In patients taking warfarin, acetaminophen is considered the analgesic of choice; however, it has been associated with increases in the international normalized ratio (INR). Regular acetaminophen use should be discouraged in patients on warfarin. Patients who require higher scheduled doses (e.g., those with osteoarthritis) should have their INR monitored and warfarin dose adjusted as acetaminophen doses are titrated.

Table 5–5 Clinically Important Drug-Drug Interactions With Nonprescription Analgesic Agents

Analgesic/ Antipyretic	Interactive Drug	Potential Interaction	Management/Preventive Measure(s)
Acetaminophen	Alcohol	Increased risk of hepatotoxicity	Avoid concurrent use if possible; minimize alcohol intake when using acetaminophen.
Acetaminophen	Warfarin	Increased risk of bleeding (elevations in INR)	Limit acetaminophen to occasional use; monitor INR for several weeks when acetaminophen 2–4 g daily is added or discontinued in patients on warfarin.

Analgesic/ Antipyretic	Interactive Drug	Potential Interaction	Management/Preventive Measure(s)
Aspirin	Valproic acid	Displacement from protein-binding sites and inhibition of valproic acid metabolism	Avoid concurrent use; use naproxen instead of aspirin (no interaction).
Aspirin	NSAIDs, including COX-2 inhibitors	Increased risk of gastroduodenal ulcers and bleeding	Avoid concurrent use if possible.
Salicylates	Live influenza virus vaccine	Risk of Reye syndrome in children and adolescents	Avoid concurrent administration in children younger than 18 years.
Ibuprofen	Aspirin	Decreased antiplatelet effect of aspirin	Aspirin should be taken at least 60 minutes before or 8 hours after ibuprofen. Use acetaminophen (or other analgesic) instead of ibuprofen.
Ibuprofen	Phenytoin	Displacement from protein-binding sites	Monitor free phenytoin levels; adjust dose as indicated.
Salicylates and other NSAIDs	Bisphosphonates	Increased risk of GI or esophageal ulceration	Use caution with concomitant use.
NSAIDs	Digoxin	Renal clearance of digoxin inhibited	Monitor digoxin levels; adjust dose as indicated.
Salicylates and other NSAIDs	Agents with antiplatelet properties (SSRIs, NSAIDs, P2Y12 inhibitors)	Increased risk of bleeding	Monitor therapy
Salicylates and other NSAIDs	Antihypertensive agents, beta blockers, ACE inhibitors, vasodilators, diuretics	Antihypertensive effect inhibited; possible hyperkalemia with potassium-sparing diuretics and ACE inhibitors	Monitor blood pressure, cardiac function, and potassium levels.
Salicylates and other NSAIDs	Anticoagulants	Increased risk of bleeding, especially GI	Avoid concurrent use, if possible.

Analgesic/ Antipyretic	Interactive Drug	Potential Interaction	Management/Preventive Measure(s)
Salicylates and other NSAIDs	Alcohol	Increased risk of GI bleeding	Avoid concurrent use, if possible; minimize alcohol intake when using salicylates and NSAIDs.
Salicylates and other NSAIDs	Methotrexate	Decreased methotrexate clearance	Avoid salicylates and NSAIDs with high-dose methotrexate therapy; monitor levels with concurrent treatment.
Salicylates (moderate-high doses)	Sulfonylureas	Increased risk of hypoglycemia	Avoid concurrent use, if possible; monitor blood glucose levels when changing salicylate dose.

Key: ACE = Angiotensin-converting enzyme; COX = cyclooxygenase; GI = gastrointestinal; INR = international normalized ratio;

NSAIDs = nonsteroidal anti-inflammatory drugs; SSRIs = selective serotonin reuptake inhibitors.

Source: [Reference 24](#).

Nonsalicylate Nonsteroidal Anti-inflammatory Drugs

NSAIDs relieve pain through central and peripheral inhibition of cyclooxygenase (COX) with consequent inhibition of prostaglandin synthesis.

All nonprescription NSAIDs are rapidly absorbed from the GI tract, with consistently high degree of bioavailability. They are extensively metabolized, mainly by glucuronidation, to inactive compounds in the liver. Elimination occurs primarily through the kidneys. Time to onset of activity for naproxen sodium and ibuprofen is approximately 30 minutes. Duration of activity is up to 12 hours for naproxen sodium and 6–8 hours for ibuprofen. FDA-approved uses for nonprescription NSAIDs include reducing fever and relieving minor pain associated with headache, the common cold, toothache, muscle ache, backache, arthritis, and menstrual cramps. NSAIDs have analgesic, antipyretic, and anti-inflammatory activity, and they are useful in managing mild to moderate pain of nonvisceral origin. Ibuprofen and naproxen sodium and became available for nonprescription use in 1984 and 1994, respectively, and

both are propionic acid derivatives. Although FDA has approved ketoprofen for nonprescription use, no commercially available nonprescription analgesics currently contain this agent.

Recommended child and adult dosages of nonprescription NSAIDs are provided in [Tables 5–2](#) and [5–3](#). [Table 5–6](#) lists selected trade-name products. Ibuprofen is available as a liquid for pediatric use and comes in two different strengths (50 mg/1.25 mL and 100 mg/5 mL). This dual option may contribute to the potential for dosing errors. A dose–effect relationship has been demonstrated for ibuprofen analgesia in the range of 100–400 mg.

Table 5–6 Selected Single-Entity Nonprescription Nonsalicylate Nonsteroidal Anti-inflammatory Drugs	
Trade Name	Primary Ingredient
Ibuprofen Products: Pediatric Formulations	
Children’s Advil Suspension	Ibuprofen 100 mg/5 mL
Children’s Motrin Suspension	Ibuprofen 100 mg/5 mL
Motrin Infants’ Drops Suspension	Ibuprofen 50 mg/1.25 mL
Junior Strength Advil Chewable Tablet	Ibuprofen 100 mg
Ibuprofen Products: Adult Formulations	
Advil tablet/capsule	Ibuprofen 200 mg
Motrin IB Ibuprofen tablet	Ibuprofen 200 mg
Advil Migraine capsule	Ibuprofen 200 mg
Naproxen Products	
Aleve tablet/capsule	Naproxen sodium 220 mg
Mediproxen tablet	Naproxen sodium 220 mg
All Day Relief tablet	Naproxen sodium 220 mg

The most frequent adverse effects of NSAIDs involve the GI tract and include

dyspepsia, heartburn, nausea, anorexia, and epigastric pain. NSAIDs may be taken with food, milk, or antacids if upset stomach occurs. Tablets should be taken with a full glass of water, suspensions should be shaken thoroughly, and enteric-coated or sustained-release preparations should never be crushed or chewed. Other adverse effects include dizziness, fatigue, headache, and nervousness. Rashes or pruritus (itching), photosensitivity, and fluid retention or edema may occur in some patients; at normal doses, however, these effects usually are rare.

GI ulceration, perforation, and bleeding are serious potential complications of NSAID use. Risk factors include age older than 60 years, previous ulcer disease, concurrent use of anticoagulants (including aspirin), higher dose or longer duration of treatment, and consumption of three or more alcoholic drinks per day. Product labeling for NSAIDs includes warnings about stomach bleeding with adult doses (see the box “A Word About NSAIDs and Stomach Bleeding”).³⁶ Labeling for prescription products that contain ibuprofen and naproxen includes the following warning:

NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

NSAID use is associated with increased risk for myocardial infarction (MI), heart failure, hypertension, and stroke. While not completely understood, the pathophysiologic mechanism for increased cardiovascular risk includes increased thromboxane A₂ activity and suppressed vascular prostacyclin synthesis, resulting in vasoconstriction and platelet aggregation. The cardiovascular risk associated with nonselective NSAIDs appears to depend on dose and duration; people with underlying risk factors such as hypertension, heart failure, and diabetes are at greater risk. Limited data suggest that the risk may not be the same for all nonselective NSAIDs.³⁷

The American Heart Association recommends that patients with cardiovascular disease or those at high risk for cardiac events (e.g., hyperlipidemia, hypertension, diabetes, other macrovascular disease) avoid NSAIDs. Patients at low cardiac risk should nevertheless exercise caution with use of NSAIDs by taking the minimum dose for the shortest duration needed to control symptoms. Clinical evidence has shown that the use of NSAIDs in

patients with a history of MI is associated with an increased risk of future cardiovascular events, extending indefinitely.³⁸ Labeling for prescription products that contain ibuprofen and naproxen includes the following warning²⁴:

NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Ibuprofen and naproxen tablets are contraindicated for treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery. NSAIDs may decrease renal blood flow and glomerular filtration rate through inhibition of renal prostaglandin synthesis. Consequently, blood urea nitrogen and serum creatinine levels can increase, often with concomitant sodium and water retention. Advanced age, hypertension, diabetes, atherosclerotic cardiovascular disease, and use of diuretics appear to increase the risk of renal toxicity with ibuprofen use. Congestive heart failure may be exacerbated by the use of NSAIDs because of sodium and water retention, increased systemic vascular resistance, and impaired response to diuretics.³⁹ Therefore, patients with a history of impaired renal function, congestive heart failure, or diseases that compromise renal hemodynamics should not self-treat with NSAIDs.

Clinically important drug–drug interactions of NSAIDs are listed in [Table 5–5](#). Ibuprofen increases bleeding time by reversibly inhibiting platelet aggregation. Patients on aspirin for cardiovascular prophylaxis should take it at least 1 hour before or 8 hours after ibuprofen to avoid a pharmacodynamic interaction that inhibits the antiplatelet effect of aspirin. Ibuprofen should not be recommended for self-treatment in patients who concurrently are taking anticoagulants, because its antiplatelet activity could increase GI bleeding. Owing to concerns regarding decreased cardiovascular protection and increased bleeding risk, great caution is warranted in combining aspirin and ibuprofen.

Patients who ingest three or more alcoholic drinks per day should be cautioned about the increased risk of adverse GI events, including stomach bleeding. They also should be referred to a primary care provider for monitoring of their NSAID use.

NSAID overdoses usually are associated with minimal signs and symptoms of toxicity and are rarely fatal. GI manifestations are common and include nausea, vomiting, abdominal pain, and diarrhea. The most serious effects of large NSAID overdoses include renal failure, neurologic toxicity, and acid–base changes. Examples of specific neurologic symptoms are drowsiness, changes in vision, headache, and confusion. Convulsions have been reported in children who have taken an overdose of ibuprofen. Case reports of GI bleeding also exist.⁴⁰

A Word About NSAIDs and Stomach Bleeding

The following label wording is required for the FDA warning concerning stomach bleeding for nonprescription products that contain NSAIDs in adult doses:

Stomach bleeding warning: This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if you

- have had stomach ulcers or bleeding problems
- take a blood-thinning (anticoagulant) or steroid drug
- take other drugs containing prescription or nonprescription NSAIDs (aspirin, ibuprofen, naproxen, or others)
- take more or for a longer time than directed
- are age 60 or older
- have three or more alcoholic drinks every day while using this product

Ask a doctor before use if the stomach bleeding warning applies to you:

- You have a history of stomach problems, such as heartburn.
- You have high blood pressure, heart disease, liver cirrhosis, or kidney disease.
- You are taking a diuretic.

Stop use and ask a doctor if

- You experience any of the following signs of stomach bleeding:
 - feel faint

- vomit blood
- have bloody or black stools
- have stomach pain that does not get better

Key: FDA = U.S. Food and Drug Administration; NSAID = nonsteroidal anti-inflammatory drug.

Source: [Reference 36](#).

Salicylates

Salicylates inhibit prostaglandin synthesis from arachidonic acid by inhibiting both isoforms of the COX enzyme (COX-1 and COX-2). The resulting decrease in prostaglandins reduces the sensitivity of pain receptors to the initiation of pain impulses at sites of inflammation and trauma. Although some evidence suggests that aspirin also produces analgesia through a central mechanism, its site of action is primarily peripheral.

Salicylates are absorbed by means of passive diffusion of the nonionized drug in the stomach and small intestine. Factors affecting absorption include dosage form, gastric pH, gastric emptying time, dissolution rate, and the presence of antacids or food. Absorption from immediate-release aspirin products is complete. Rectal absorption of a salicylate suppository is slow and unreliable, as well as proportional to rectal retention time.

Once absorbed, aspirin is hydrolyzed in the plasma to salicylic acid in 1–2 hours. Salicylic acid is widely distributed to all tissues and fluids in the body, including central nervous system tissue, breast milk, and fetal tissue. Protein binding is concentration-dependent. At concentrations lower than 100 mg/mL, approximately 90% of salicylic acid is bound to albumin, whereas at concentrations greater than 400 mg/mL, approximately 75% is bound. Salicylic acid is largely eliminated through the kidney. Urine pH determines the amount of unchanged drug that is eliminated, with urinary concentrations increasing substantially in more alkaline urine (pH ~8).

Dosage form alterations include enteric coating, buffering, and sustained release. These formulations were developed to change the rate of absorption

and/or to reduce the potential for GI toxicity. Enteric-coated aspirin is absorbed only from the small intestine; its absorption is markedly slowed by food, which is attributed to prolonged gastric emptying time. Hypochlorhydria from acid-suppressing agents (especially proton pump inhibitors) may result in dissolution of enteric-coated products in the stomach, negating any potential benefit in preventing local gastric irritation. For patients requiring rapid pain relief, enteric-coated aspirin is inappropriate because of the delay in absorption and time to onset of analgesic effect.

Buffered aspirin products are available in both tablet and effervescent forms. Although buffered products are absorbed more rapidly than nonbuffered products, time to onset of effect is not improved appreciably. Common buffers include aluminum hydroxide; magnesium carbonate, hydroxide, or oxide; calcium carbonate; and sodium bicarbonate (in effervescent formulations). Some effervescent aspirin solutions contain large amounts of sodium and must be avoided by patients who require restricted sodium intake (such as those with hypertension, heart failure, or renal failure). Sustained-release aspirin is formulated to prolong duration of action by slowing dissolution and absorption. Other salicylates approved for nonprescription use are magnesium salicylate and sodium salicylate. Currently, sodium salicylate is not available in a commercial product; however, magnesium salicylate is available as a tablet.

FDA-approved uses for salicylates include treatment of symptoms for osteoarthritis, rheumatoid arthritis, and other rheumatologic diseases, as well as temporary relief of minor aches and pains associated with backache or muscle aches. Salicylates also are effective in treating mild to moderate pain from musculoskeletal conditions and fever.

Because of its inhibitory effects on platelet function, aspirin is also used for prevention of thromboembolic events (e.g., MI, stroke) in high-risk patients. Unlike with the NSAIDs previously discussed, this inhibitory effect is irreversible for aspirin. Thus, the inhibition continues for the duration of the platelet's life. With NSAIDs, the duration of inhibition depends on factors such as dose, serum level, and half-life. Aspirin's use for prophylaxis against MI and other forms of ischemic cardiovascular disease must be guided by a primary care provider. In March 2019, the American College of Chest Physicians and the American Heart Association issued a Guideline on the Primary Prevention of Cardiovascular Disease.⁴¹ The guideline provides evidence-based recommendations for decreasing the risk of developing atherosclerotic

cardiovascular disease (ASCVD). Adults aged 40–75 years should be screened to determine their estimated 10-year risk of developing ASCVD. Online risk assessment tools are available to quantify this risk (http://tools.acc.org/ldl/ascvd_risk_estimator/index.html#!/calculate/estimator/).⁴²

The use of aspirin for ASCVD prevention is discussed in the guideline. On the basis of recent findings, the guidelines state that aspirin use for primary prevention is not recommended for most patients. For some patients at high risk for development of ASCVD coupled with a low risk for bleeding, the use of low-dose aspirin (75–100 mg orally daily) may be recommended. Patients older than age 70 are at increased risk for bleeding and should not routinely receive aspirin for primary prevention, nor should patients of any age identified as being at increased risk for bleeding.

The decision to use low-dose aspirin for primary prevention must consider risk factors for developing a cardiac event and risk factors for bleeding. The guideline includes a list of factors that may favor the use of aspirin including family history of early MI; inability to achieve goals for lipids, blood pressure, or glucose; or significant elevation of coronary artery calcium score. The guideline also includes a list of factors that may signify a greater risk of bleeding from aspirin, including a history of GI bleeding or peptic ulcer disease, bleeding at other sites, age older than 70 years, thrombocytopenia, coagulopathy, chronic kidney disease, use of medications that increase the risk of bleeding such as NSAIDs, steroids, direct oral anticoagulants, and warfarin. As noted by the guideline authors, these lists are not exhaustive, however, and a careful patient-specific analysis of the potential risks and benefits must include consideration of the patient’s understanding of the decision.⁴¹ Recommended child and adult dosages of nonprescription salicylates are provided in [Tables 5–2](#) and [5–3](#). [Table 5–7](#) provides selected salicylate products. Aspirin dosages of 4–6 g daily usually are needed to produce anti-inflammatory effects. The maximum analgesic dosage for self-medication with aspirin is 4 g daily; therefore, anti-inflammatory activity often will not occur unless the drug is used at the high end of the acceptable dosage range.

Table 5–7 Selected Adult Formulations of Nonprescription Single-Entity Salicylate Products

Trade Name	Primary Ingredient
Bayer Low-Dose Aspirin tablet	Aspirin 81 mg

Trade Name	Primary Ingredient
St. Joseph Chewable Aspirin 81 mg tablet	Aspirin 81 mg
Ecotrin Enteric-Coated tablet	Aspirin 325 mg
Bayer Aspirin Delayed Release tablet	Aspirin 325 mg
Bayer Plus Extra Strength tablet	Aspirin 500 mg
DeWitts Pain Reliever tablet	Magnesium salicylate 325 mg
Extra Strength Doan's tablet	Magnesium salicylate tetrahydrate 580 mg
Percogesic Maximum Strength Backache Relief Coated caplet/tablet	Magnesium salicylate tetrahydrate 580 mg

Aspirin is known to commonly cause dyspepsia, which may be minimized by taking it with food. In addition, aspirin is associated with development of gastritis and ulceration of the upper GI tract. It produces GI mucosal damage by compromising the protective mucous and bicarbonate layers of the gastric mucosa, thereby permitting back-diffusion of acid, with consequent cellular damage and vascular erosion. Two distinct mechanisms are involved: (1) a local irritant effect resulting from contact of the medication with the gastric mucosa and (2) a systemic effect from prostaglandin inhibition. Lack of upper abdominal pain or discomfort is not a reliable indicator for the absence of GI damage associated with use of NSAIDs.^{43,44}

The use of aspirin has been shown to increase the risk for serious upper GI events two- to fourfold.⁴³ Patients with risk factors for upper GI bleeding should avoid self-treatment with aspirin. Recognized risk factors are (1) history of stomach bleeding or ulcers; (2) age older than 60 years; (3) concomitant use of NSAIDs, anticoagulants, antiplatelet agents, or systemic corticosteroids; (4) infection with *Helicobacter pylori*; (5) consumption of three or more alcoholic drinks per day; and (6) use for longer than directed.^{36,45} Use of aspirin products with enteric coating may reduce the impact of local gastric irritation. However, presence of enteric coating or buffering does not decrease the risk of serious GI toxicity because it is caused by a systemic effect of reduced production of prostaglandins that are important in maintaining the protective lining of the

GI tract.

Serious aspirin intolerance is uncommon and consists of two types: *cutaneous* (manifesting as urticaria and angioedema) and *respiratory* (manifesting as bronchospasm, laryngospasm, and rhinorrhea). The mechanism is not immunologically mediated. Risk factors for serious aspirin intolerance include chronic urticaria for the cutaneous type and asthma with nasal polyps for the respiratory type. Ten percent of people diagnosed with asthma have aspirin sensitivity.⁴⁶ The degree of intolerance is variable, ranging from minor to severe. Patients with aspirin intolerance generally are advised to avoid NSAIDs. However, the nonacetylated salicylates (magnesium salicylate) and acetaminophen are considered safe.⁴⁶

Nonprescription salicylates interact with several other important drugs and drug classes. Clinically important drug interactions of salicylates are listed in [Table 5–5](#). When monitoring therapy in patients who are taking high-dose salicylates, health care providers should review current drug interaction references for newly identified interactions.

Aspirin ingestion may produce a positive result on fecal occult blood testing, so its use should be discontinued at least 3 days before testing. Similarly, aspirin should be discontinued 2–7 days before surgery and should not be used to relieve pain after tonsillectomy, dental extraction, or other surgical procedures, except under the close supervision of a primary care provider. Aspirin can potentiate bleeding from capillary-rich sites such as the GI tract, tonsillar beds, and tooth sockets.

Because of its effect on hemostasis, aspirin is contraindicated in patients with hypoprothrombinemia, vitamin K deficiency, hemophilia, history of any bleeding disorder, or history of peptic ulcer disease. In patients with compromised renal function, renal excretion of magnesium may be decreased, allowing accumulation of toxic levels with regimens including magnesium salicylate. The maximum 24-hour dose of magnesium salicylate delivers 400 mg of magnesium.

All salicylates should be avoided in patients with a history of gout or hyperuricemia because of dose-related effects on renal uric acid handling. In such patients, taking low-dose aspirin for 2 consecutive days is associated with increased risk for onset or reemergence of gout. Serum urate monitoring should be considered in patients with gout who are receiving aspirin

therapy.⁴⁷

Reye syndrome is an acute illness occurring almost exclusively in children and teenagers.⁴⁸ The cause is unknown, but the use of salicylates to treat viral illnesses has been associated with the syndrome. Onset usually follows a viral infection with influenza (type A or B) or varicella (chickenpox). *Reye syndrome* is characterized by progressive neurologic damage, fatty liver with encephalopathy, and hypoglycemia. Neurologic manifestations may start with lethargy and progress to delirium, confusion, and seizures. The mortality rate may be as high as 50%.

The American Academy of Pediatrics, FDA, the Centers for Disease Control and Prevention, and the Surgeon General have issued warnings that aspirin and other salicylates (including bismuth subsalicylate and nonaspirin salicylates) should be avoided in children and teenagers who have influenza or chickenpox. The following statement is included in the Electronic Code of Federal Regulations⁴⁸ and is required on labeling for nonprescription aspirin and aspirin-containing products:

Reye's syndrome: Children and teenagers who have or are recovering from chickenpox or flu-like symptoms should not use this product. When using this product, if changes in behavior with nausea and vomiting occur, consult a doctor because these symptoms could be an early sign of Reye's syndrome, a rare but serious illness.

Although a simple viral upper respiratory infection does not contraindicate aspirin use, differentiation of its symptoms from those of influenza and chickenpox can be difficult. Many health care providers recommend a conservative approach of avoiding aspirin whenever influenza-like symptoms are present. Use of aspirin as a pediatric antipyretic and reports of *Reye syndrome* have all but ceased in the United States.

All nonprescription analgesic and antipyretic products for adult use bear a warning regarding alcohol use. Use of aspirin with alcohol intake increases the risk of adverse GI events, including stomach bleeding. Patients who consume three or more alcoholic drinks daily should be counseled about the associated risks and referred to their primary care provider before they use aspirin.

Mild salicylate intoxication (*salicylism*) occurs with chronic toxic blood levels, generally achieved in adults who take 90–100 mg/kg per day of a salicylate for

at least 2 days. Symptoms and signs of salicylate toxicity include headache, dizziness, tinnitus, difficulty hearing, dimness of vision, mental confusion, lassitude, drowsiness, sweating, thirst, hyperventilation, nausea, vomiting, and occasional diarrhea. These clinical abnormalities all can be reversed by lowering the plasma concentration to a therapeutic range. Tinnitus, typically an early manifestation, should not be used as a sole indicator of salicylate toxicity.

Acute salicylate intoxication is categorized as mild (associated with ingestion of <150 mg/kg), moderate (with ingestion of $150\text{--}300$ mg/kg), or severe (with ingestion of >300 mg/kg). Clinical manifestations depend on the plasma drug concentration and may include lethargy, nausea, vomiting, dehydration, tinnitus, hemorrhage, tachypnea and pulmonary edema, convulsions, and coma. Acid-base disturbances are prominent and range from respiratory alkalosis to metabolic acidosis. Initially, salicylate affects the respiratory center in the medulla, producing hyperventilation and respiratory alkalosis. In severely intoxicated adults and in most salicylate-poisoned children younger than 5 years, respiratory alkalosis progresses rapidly to metabolic acidosis. Children are more likely than adults to exhibit high fever in salicylate poisoning. Hypoglycemia resulting from increased glucose utilization may be especially serious in children. Bleeding may occur from the GI tract or mucosal surfaces, and petechiae are a prominent feature at autopsy in fatal cases.

Emergency management of acute salicylate intoxication is directed at preventing absorption of salicylate from the GI tract and providing supportive care. Activated charcoal should be used at home only if recommended by poison control center or emergency medical services personnel. In a hospital emergency department setting, GI tract decontamination with gastric lavage or activated charcoal may be undertaken. Enhancing renal elimination can be accomplished through alkalinization of the urine. Dosing recommendations for the use of activated charcoal are included in [Chapter 21](#).

Combination Products

Many nonprescription analgesics are available in combination products ([Table 5–8](#)).

Table 5–8 Selected Nonprescription Combination Analgesic Products

Trade Name	Primary Ingredient(s)
Acetaminophen-Containing Products	
Excedrin Tension Headache caplet	Acetaminophen 500 mg; caffeine 65 mg
Excedrin PM Headache caplet	Acetaminophen 250 mg; aspirin 250 mg; diphenhydramine 38 mg
Goody's Headache Relief Shot Liquid	Acetaminophen 1000 mg; caffeine 65 mg
Percogesic Original Strength tablet	Acetaminophen 325 mg; diphenhydramine 12.5 mg
Percogesic Extra Strength tablet	Acetaminophen 500 mg; diphenhydramine 12.5 mg
Sudafed PE Pressure + Pain caplet	Acetaminophen 325 mg; phenylephrine 5 mg
Tylenol PM caplet	Acetaminophen 500 mg; diphenhydramine 25 mg
Tylenol Sinus + Headache caplet	Acetaminophen 325 mg; phenylephrine 5 mg
Tylenol Sinus Severe caplet	Acetaminophen 325 mg; phenylephrine 5 mg; guaifenesin 200 mg
Nonsalicylate NSAID-Containing Products	
Advil Cold & Sinus tablet (behind the counter)	Ibuprofen 200 mg; pseudoephedrine 30 mg
Advil Allergy and Congestion Relief coated tablet	Ibuprofen 200 mg; phenylephrine 10 mg; chlorpheniramine maleate 4 mg
Advil Sinus Congestion and Pain tablet	Ibuprofen 200 mg; phenylephrine 10 mg
Aleve-D Sinus & Headache caplet (behind the counter)	Naproxen sodium 220 mg; pseudoephedrine 120 mg
Motrin PM caplet	Ibuprofen 200 mg; diphenhydramine 38 mg
Sudafed 12 Hour Pressure + Pain Extended Release tablet (behind the counter)	Naproxen sodium 220 mg; pseudoephedrine 120 mg
Aspirin-Containing Products	

Trade Name	Primary Ingredient(s)
Anacin Regular Strength tablet	Aspirin 400 mg; caffeine 32 mg
Bayer Cafiaspirina caplet	Aspirin 500 mg; caffeine 40 mg
Excedrin Migraine caplet	Aspirin 250 mg; acetaminophen 250 mg; caffeine 65 mg
Goody's Cool Orange Powder	Aspirin 500 mg; acetaminophen 325 mg; caffeine 65 mg
Goody's Extra Strength Headache Powder	Aspirin 520 mg; acetaminophen 260 mg; caffeine 32.5 mg

Key: NSAID = Nonsteroidal anti-inflammatory drug.

Caffeine is used as an adjunct to analgesics for tension-type and migraine headaches. It also may have its own analgesic properties, and curbing or ceasing caffeine consumption is known to cause withdrawal headache when it is taken regularly. Clinical trials have suggested that combining caffeine with analgesics may result in better efficacy.⁴⁹ Of note, however, caffeine itself may be a trigger for migraines, and withdrawal of caffeine, as stated, may result in headache. Combination dosage formulations containing a decongestant and either acetaminophen or an NSAID also are available. Use of such combinations appears to be logical in sinus headaches or other indications for which both analgesia and decongestion are needed.

Combinations of NSAIDs such as aspirin and/or acetaminophen may achieve goals of pain relief with lower doses of the individual agents; however, insufficient evidence is available to support the safety and effectiveness of this practice. Dosing limits for combination products should be closely monitored.

Pharmacotherapeutic Comparison

Aspirin Versus Nonacetylated Salicylates

Although definitive clinical data are lacking, aspirin and non-acetylated salicylates are believed to be of equal anti-inflammatory potency; however,

aspirin is thought to be a superior analgesic and antipyretic. With all analgesics, individual patients may respond better to one agent than to another.

Aspirin Versus Acetaminophen

Numerous controlled studies have demonstrated the equivalent analgesic efficacy of aspirin and acetaminophen on a milligram-for-milligram basis; however, statistical methods used to compare effectiveness among different studies show that acetaminophen may not be as effective in some types of pain in which an inflammatory component predominates.⁵⁰ A recent systematic review found a lack of evidence for effectiveness of acetaminophen for osteoarthritis.⁵¹

Aspirin Versus Nonsalicylate NSAID

Ibuprofen has been shown to be at least as effective as aspirin in treating various types of pain, including dental extraction pain, dysmenorrhea, and episiotomy pain. Because aspirin must be dosed at levels near the self-care maximum to achieve anti-inflammatory effects, nonsalicylate NSAIDs may be preferred for self-treatment of inflammatory disorders such as rheumatoid arthritis or acute muscle injury.⁵⁰ Nonsalicylate NSAIDs have a safety advantage of lower toxicity in overdose.

NSAID Versus Acetaminophen

For episodic tension-type headache, acetaminophen 1000 mg appears to provide relief equivalent to that achieved with naproxen 375 mg.⁵² For moderate to severe dental or sore throat pain in children, single doses of acetaminophen 7–15 mg/kg produced pain relief similar to that with ibuprofen 4–10 mg/kg. Ibuprofen was a more effective antipyretic, and both drugs were well tolerated.⁵³ A review of evidence comparing ibuprofen with acetaminophen for headache treatment in children and adults found that only two trials had shown a modest advantage for ibuprofen, and the researchers concluded that the two agents should be considered equally effective.⁵⁴ Acetaminophen does not have anti-inflammatory properties, which limits its effectiveness in inflammatory conditions, including dysmenorrhea and osteoarthritis.⁵⁰ NSAIDs are less toxic than acetaminophen in the case of an overdose.

Naproxen Versus Ibuprofen

Naproxen sodium 220 mg and ibuprofen 200 mg appear to have similar efficacy. The time to onset of activity also is similar for these two NSAIDs. Duration of action of naproxen is longer than that of ibuprofen, with a dosing schedule of every 8–12 hours versus ibuprofen's dosing schedule of every 4–6 hours. Individual patients may report a better response to one NSAID than to another, for reasons that are unclear.

Product Selection Guidelines

Special Population Considerations

Age is an important consideration in the selection of an appropriate nonprescription medication for self-treatment for headache.

Parents of children younger than 8 years should consult a pediatrician before giving their children nonprescription medications. After appropriate evaluation, children 2 years and older may use acetaminophen or ibuprofen. Children 12 years and older may use naproxen. To decrease the risk of Reye syndrome, parents should not use aspirin or aspirin-containing products in children and teenagers unless directed to do so by a primary care provider.

Older patients are at increased risk for many adverse effects of salicylates and NSAIDs. Comorbid conditions, impaired renal function, and concurrent use of other medications contribute to the increased risk. These patients are more vulnerable to serious GI toxicity and the hypertensive and renal effects of salicylates and NSAIDs. Acetaminophen may be the safest alternative in the geriatric population.

Many safety considerations have been raised regarding the use of these medications in patients who are pregnant or breastfeeding; however, no such considerations apply for males and females of reproductive potential in general. (See the Preface for a detailed explanation of the pregnancy data.) Acetaminophen crosses the placenta but is considered safe for use during pregnancy. Acetaminophen appears in breast milk, producing a milk-to-maternal plasma ratio of 0.5:1. A maternal dose of 1 g correlates with an estimated maximum infant dose that is 1.85% of the maternal dose. The only adverse effect reported in infants exposed to acetaminophen through breast milk is a rarely occurring maculopapular rash, which subsides upon drug

discontinuation. Acetaminophen use is considered compatible with breastfeeding.⁵⁵

No evidence exists that NSAIDs are teratogenic in either humans or animals. Use of these agents is contraindicated during the third trimester of pregnancy, however, because all potent prostaglandin synthesis inhibitors can cause delayed parturition, prolonged labor, and increased postpartum bleeding. These agents also can have adverse fetal cardiovascular effects (e.g., premature closure of the ductus arteriosus) when used in pregnancy (particularly in late pregnancy). Reproductive animal studies have not shown evidence of harm to the fetus; however, adequate studies to verify safety have not been conducted in humans. Use in pregnancy should be limited to clinical situations in which the potential benefit justifies potential risk to the fetus.^{55,56}

Ibuprofen is considered the safest analgesic for use by nursing mothers. This designation is based on the low concentration of ibuprofen in breast milk and the lack of reported ill effects with use of ibuprofen in infants. The concentration of ibuprofen found in breast milk has been found to be less than 1% of the recommended infant dose.²⁴ Nursing mothers should not use naproxen, however. The naproxen anion has been measured in human milk, where it accumulates at a level of 1% of the maximum plasma concentration for naproxen. Prostaglandin-inhibiting drugs have the potential to cause harm in neonates; therefore, this level of exposure in milk has led to the labeling statement to avoid use during lactation.⁵⁶

Aspirin should be avoided during pregnancy, especially during the last trimester, and during breastfeeding. Its ingestion during pregnancy may be associated with maternal adverse effects such as anemia, antepartum or postpartum hemorrhage, and prolonged gestation and labor. Regular aspirin ingestion during pregnancy may increase the risk for complicated deliveries, including unplanned cesarean section, breech delivery, and forceps delivery. Definitive data supporting these concerns, however, are lacking.

Aspirin readily crosses the placenta and can be found in higher serum concentrations in the neonate than in the mother. Salicylate elimination is slow in neonates because of the liver's immaturity and underdeveloped capacity to form glycine and glucuronic acid conjugates and because of reduced urinary excretion resulting from low glomerular filtration rates.

Fetal effects from in utero aspirin exposure include intrauterine growth

retardation, congenital salicylate intoxication, decreased albumin-binding capacity, and increased perinatal mortality. In utero death results, in part, from antepartum hemorrhage or premature closure of the ductus arteriosus. In utero aspirin exposure within 1 week of delivery can result in neonatal hemorrhagic episodes and/or pruritic rash. Reported neonatal bleeding complications include petechiae, hematuria, cephalhematoma, subconjunctival hemorrhage, and increased bleeding after circumcision.⁵⁵ An increased incidence of intracranial hemorrhage in premature or low-birth-weight infants associated with maternal aspirin use near the time of birth also has been reported.⁵⁵ An association between maternal aspirin ingestion and oral clefting and congenital heart disease has been noted. The relationship between maternal aspirin ingestion and congenital malformation remains unresolved, however, and studies have failed to confirm a relationship between maternal ingestion of aspirin and increased risk of fetal malformation.

Aspirin and other salicylates are excreted into breast milk in low concentrations. After single-dose oral salicylate ingestion, peak milk levels occur at approximately 3 hours, producing a milk-to-maternal plasma ratio of 3:8. Although no adverse effects on platelet function in nursing infants exposed to aspirin via breast milk have been reported, these agents still must be considered to carry a risk for such effects.⁵⁵

For patients with renal impairment, caution is indicated with use of salicylates and other NSAIDs. Clinically important alterations in renal blood flow that result in acute reduction in renal function can result from even short courses of salicylates. Referral for medical evaluation for assistance in selecting an analgesic is appropriate.

For patients with hepatic impairment, caution is warranted with use of acetaminophen. Presence of active liver disease is a risk factor for hepatic injury from this drug. Patients with hepatic impairment of any degree should use the smallest dose for the shortest duration possible. Prolonged use of this drug at high doses should be avoided.

Patient Factors

Nonprescription analgesics are available in a number of dosage forms. During patient assessment, the health care provider should determine which dosage form will provide an optimal clinical outcome. If rapid response is desired, then immediate-release oral dosage forms are preferred over coated or extended-

release forms. For patients experiencing migraine headache with severe nausea, rectal dosage forms may be needed. Liquid dosage forms often are used in children or adult patients who have difficulty swallowing tablets or capsules. Information regarding the FDA requirements for dispensing devices included in liquid nonprescription products is located in [Chapter 11](#), under “Special Populations.”

Use of ibuprofen in the pediatric population is complicated by the availability of two liquid formulations of different strengths. Unintended over- or underdosing can occur when parents switch between the concentrated drops (50 mg/1.25 mL) and the suspension (100 mg/5 mL). In addition, rapidly growing infants quickly outgrow previous dose requirements. Therefore, recalculation of the pediatric dose according to present age and body weight is recommended at the time of each treatment course.

Patients whose lifestyle encompasses significant alcohol ingestion (three or more drinks per day) should avoid self-treatment with nonprescription analgesics.

Patients with intolerance to aspirin also may experience cross-reactions with other chemicals or drugs. Up to 15% of aspirin-intolerant patients may exhibit signs of cross-reaction when exposed to tartrazine (a dye designated by the FDA-administered Food, Drug, and Cosmetic Act as FD&C Yellow 5), which can be found in many drugs and foods. Among persons documented to have the respiratory type of aspirin sensitivity, rates of cross-reaction between aspirin and acetaminophen, ibuprofen, and naproxen are 7%, 98%, and 100%, respectively. High cross-reaction rates also are reported with some prescription NSAIDs. The proposed mechanism of cross-sensitivity between aspirin and other NSAIDs involves shunting arachidonic metabolism down the lipoxygenase pathway (consequent to inhibition of the COX-1 enzyme pathway), resulting in accumulation of leukotrienes, which can cause bronchospasm and anaphylaxis. Acetaminophen and nonacetylated salicylates are weak inhibitors of COX-1 at moderate doses. Patients with a history of aspirin intolerance should therefore be advised to avoid all aspirin- and other NSAID-containing products, and to use acetaminophen or a nonacetylated salicylate, with the caveat that acetaminophen does not offer anti-inflammatory properties.

Patient Preferences

Consideration of dosing frequency in product selection may lead to improved outcomes for individual patients. Naproxen can be taken 2 or 3 times daily, which may improve patient adherence to the medication regimen. By contrast, immediate-release products of acetaminophen, ibuprofen, and salicylates may require dosing as frequently as every 4 hours. Acetaminophen 650 mg in extended-release form is given every 8 hours.

Complementary Therapies

Butterbur, feverfew, riboflavin, and coenzyme Q10 are commonly used for the prevention of migraine headaches and are discussed in depth in [Chapter 51](#). These natural products have limited efficacy for the treatment of other types of headaches. Essential oil remedies include application of peppermint oil to the forehead and temples for treatment of tension headache and inhalation of aromatized lavender oil to relieve migraine. Recent and well-designed trials to further clarify the efficacy and safety of essential oils are lacking. Magnesium and omega-3 polyunsaturated fatty acid supplementation for headache prevention also has been considered.²⁰

Acupuncture has been used to prevent migraine and tension-type headache. Evaluation of acupuncture is complicated by difficulties in blinding of study participants and investigators and by differences in identifying acupuncture points. Overall, results have been variable, but several randomized, placebo-controlled trials found acupuncture to be effective in reducing frequency and severity of headache.⁵⁶ Methods focusing on stress relief and relaxation techniques such as massage, yoga, and biofeedback therapy may be useful for the prevention and treatment of headache.²⁰ Some of these methods are discussed in more depth in [Chapter 52](#).

Assessment of Headache: A Case-Based Approach

Before self-treatment of headache can be recommended, the health care provider must assess the patient's headache complaint to determine type, severity, location, frequency, intensity over time, and age at onset. The next

step is to obtain a medical and psychosocial history. All current medications should be inventoried, and all past and present headache treatments should be reviewed, with emphasis on determining which treatments, if any, were successful or preferred.

Secondary headaches, other than minor sinus headache, are excluded from self-treatment. Headache associated with seizures, confusion, drowsiness, or cognitive impairment may be a clinical indicator of brain tumor, ischemic stroke, subdural hematoma, or subarachnoid hemorrhage. Headache accompanied by nausea, vomiting, fever, and stiff neck may indicate brain abscess or meningitis. Headache with night sweats, aching joints, fever, weight loss, and visual symptoms (e.g., blurring) in patients with rheumatoid arthritis may indicate cranial arteritis. Headache associated with localized facial pain, muscle tenderness, and limited motion of the jaw may indicate temporomandibular joint disorder.

Cases 5–1 and 5–2 illustrate assessment of two different patients with headache.

Patient Counseling for Headache

To optimize outcomes from therapy, the health care provider should instruct patients to take an appropriate dose of analgesic early in the course of the headache. The use of nonprescription analgesics to preempt or abort migraine headaches should also be explained to patients with migraines whose headaches are predictable. Patients for whom headache is a relatively common occurrence should be encouraged to keep a log of their headache episodes to document triggers, frequency, intensity, duration of episodes, and response to treatment. This record may also be helpful in identifying factors that can improve headache prevention and treatment. Patients should be advised that continuing or escalating pain can be a sign of a more serious problem and that such pain warrants prompt medical attention. Appropriate drug and nondrug measures for treating headaches should be explained in appropriate detail. Frequent use of nonprescription analgesics is not advisable because of the risk for medication overuse headache. The health care provider should convey the message that nonprescription analgesics are potent medications with accompanying potential adverse effects, interactions, and precautions and warnings. The box “Patient Education for Headache” lists

specific information for patient counseling.

Evaluation of Patient Outcomes for Headache

Appropriate follow-up evaluation will depend on headache frequency and severity, as well as patient factors. Headache pain relief should begin within 30 minutes and peak at 2 hours after administration of an over-the-counter analgesic. Patients should seek medical attention if headaches persist longer than 3 days or worsen despite self-treatment. For patients with episodic headaches, a trial of 6–12 weeks may be needed to assess efficacy of treatment. For chronic headache, follow-up evaluation after 4–6 weeks should be adequate to assess treatment efficacy. Patients with migraine headaches who do not obtain adequate relief with self-treatment should be referred for medical evaluation, because effective prescription therapies are available to substantially limit pain and disability.

Case 5–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient describes a dull ache in her forehead. She said it started a few hours ago and is interfering with her ability to concentrate on studying for an upcoming exam. It seems to feel worse when she tries to think and study for the exam. Headaches are generally uncommon for her but seem to increase in frequency during final exams.
b. Description of any factors that seem to	Closing her eyes and resting seem to help relieve the pain.

Relevant Evaluation Criteria	Scenario/Model Outcome
precipitate, exacerbate, and/or relieve the patient's symptom(s)	
c. Description of the patient's efforts to relieve the symptoms	Other than closing her eyes, the patient has not tried anything else to relieve pain.
d. Patient's identity	Cynthia Marshall
e. Patient's age, gender, height, and weight	20 years, female, 5 ft 3 in., 130 lb
f. Patient's occupation	Student
g. Patient's dietary habits	Breakfast bar for breakfast, salad from the school cafeteria for lunch, and dinner varies daily depending on schedule. She does not consume alcohol and has a single cup of coffee most mornings.
h. Patient's sleep habits	Reports sleeping 6-7 hours nightly.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Multivitamin
j. Allergies	None
k. History of other adverse reactions to medications	None
l. Other (describe) -----	n/a
Assess	
2. Differentiate patient's signs/symptoms and correctly identify the patient's primary	Ms. Marshall is experiencing a dull ache in her forehead consistent with a tension-type headache. This is likely a response to the stress of school.

Relevant Evaluation Criteria	Scenario/Model Outcome
problem(s).	
3. Identify exclusions for self-treatment.	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer Ms. Marshall to an appropriate HCP. (2) Recommend self-care with a nonprescription analgesic and nondrug measures. (3) Recommend self-care until Ms. Marshall can see an appropriate HCP. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Ms. Marshall should use a nonprescription analgesic and nondrug measures to treat her problem.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Acetaminophen, ibuprofen, and naproxen are all appropriate options. Correct dosing for the selected medication is essential, with careful attention to not take more than the recommended daily amount. Additional stress relief measures should be used when needed."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Tension-type headache can be effectively treated with nonprescription medications. Because stress is a likely trigger for the headache, it is important to focus on stress-relieving activities as well. If the medication chosen does not relieve the pain or if the pain worsens, you should see a health care provider."
Implement	

Relevant Evaluation Criteria	Scenario/Model Outcome
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	The specific administration of the medication is determined by the specific analgesic chosen. Most pain relievers will start working within about 30 minutes, and pain relief duration will depend on the analgesic used. The pain should be gone or noticeably diminished by the analgesic. Adverse effects will depend on the product chosen. All medications should be kept in a cool, dry place and out of reach of children. A headache diary will help keep track of headache frequency and help identify possible triggers.
Solicit follow-up questions from the patient or caregiver.	“Is it possible to not have these headaches while I’m in school?”
Answer the patient’s or caregiver’s questions.	“Various methods to reduce stress may help decrease the frequency of the headaches. Stress reduction measures will include appropriate study strategies and adequate sleep.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Follow-up with the patient should occur in 4–6 weeks. Owing to the episodic nature of this headache, 6 weeks may be necessary to fully evaluate the treatment.

Key: HCP = Health care provider; n/a = not applicable.

Case 5–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient’s symptoms and medical history,	

Relevant Evaluation Criteria	Scenario/Model Outcome
including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient approaches the pharmacy wearing her sunglasses. She says that she is experiencing throbbing pain on one side of her head. She is feeling a bit nauseous as well and says the pain started about 30 minutes ago.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	She said that light makes the pain worse, which is why she is wearing sunglasses. She also said that she is sensitive to sound. The only relief seems to come from resting in a dark, quiet room.
c. Description of the patient's efforts to relieve the symptoms	She has tried going to a dark and quiet location, but the pain continued. She also tried a cold towel on her face, but the pain still continued.
d. Patient's identity	Betsy Ogaku
e. Patient's age, gender, height, and weight	34 years, female, 5 ft 6 in., 150 lb
f. Patient's occupation	Real estate agent
g. Patient's dietary habits	Egg white wrap for breakfast, salad with grilled chicken for lunch, and a well-rounded dinner each evening.
h. Patient's sleep habits	About 7 hours each evening
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Citalopram 20 mg once daily for depression Levothyroxine 137 mcg for hypothyroidism Tums as needed for occasional heartburn No dietary supplements
j. Allergies	Penicillin
k. History of other adverse reactions to medications	None
l. Other (describe) _____	n/a
Assess	

Relevant Evaluation Criteria	Scenario/Model Outcome
2. Differentiate patient's signs/symptoms and correctly identify the patient's primary problem(s).	Mrs. Ogaku is suffering from unilateral, throbbing pain associated with sensitivity sound and light. She additionally is experiencing nausea. These symptoms are caused by migraine.
3. Identify exclusions for self-treatment.	Symptoms consistent with migraine, but no formal diagnosis of migraine headache.
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer Mrs. Ogaku to an appropriate HCP. (2) Recommend self-care with a nonprescription analgesic and nondrug measures. (3) Recommend self-care until Mrs. Ogaku can see an appropriate HCP. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Mrs. Ogaku should see a health care provider.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"You should see your primary care provider for treatment."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"This option is best because you are experiencing a migraine headache. Self-treatment with over-the-counter medications is not recommended for a migraine until you have been evaluated and diagnosed by your primary care provider."
Implement	
8. When recommending self-care with	"Work with your primary care provider to

Relevant Evaluation Criteria	Scenario/Model Outcome
nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	determine the cause of this migraine. Try to implement lifestyle changes to prevent a future occurrence.”
Solicit follow-up questions from the patient or caregiver.	“Does this mean that I will continue to have this problem in the future?”
Answer the patient’s or caregiver’s questions.	“The frequency of migraine headache varies for each affected person. A thorough understanding of the cause of your migraine will help you try to prevent another in the future.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact the patient the following day to ensure that she made an appointment with a primary care provider.

Key: HCP = Health care provider.

Patient Education for Headache

The objectives of self-treatment are (1) to relieve headache pain, (2) to prevent headaches when possible, and (3) to prevent medication overuse headaches by avoiding chronic use of nonprescription analgesics. Carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

Tension-Type Headaches

- Nonprescription pain relievers (analgesics) are usually effective in relieving tension-type headaches. However, consult your primary care provider before using such medications for chronic tension-

type headaches that occur 15 days per month or more often over a 3-month period.

- If nonprescription pain relievers are used for chronic headaches, keep records of how often they are used, and share this information with your primary care provider.

Migraine Headache

- Avoid substances (food, caffeine, alcohol, medications) or situations (stress, fatigue, oversleeping, fasting, missing meals) that you know can trigger a migraine.
- Use the following nutritional strategies to prevent migraine:
 - Avoid foods or food additives known to trigger migraines, including red wine, aged cheese, aspartame, monosodium glutamate, coffee, tea, cola beverages, and chocolate.
 - Avoid foods to which you are allergic.
 - Eat regularly to avoid hunger and low blood sugar.
- If onset of migraines is predictable (e.g., occurrence of headache during menstruation), take aspirin, ibuprofen, or naproxen to prevent the headache. Start taking the analgesic 2 days before you expect the headache and continue regular use during the time the headache might start.
- Try to stop a migraine by taking an NSAID such as aspirin or acetaminophen at the onset of headache pain.
- If desired, rest in a quiet, dark room and use an ice bag or cold pack applied with pressure to the forehead or temples to reduce the pain associated with acute migraine attacks.

Sinus Headache

- Consider using a combination of a decongestant and a nonprescription analgesic to relieve the pain of sinus headache.

Precautions for Nonprescription Analgesics

- If you are pregnant or breastfeeding, consult your primary care provider before taking any nonprescription medications.

- If you have a medical condition or are taking prescription medications, obtain medical advice before taking any of these medications. Nonprescription analgesics are known to interact with several medications.
- Do not take nonprescription analgesics more often than 3 days per week unless a health care provider has recommended prolonged use.
- Do not take these medications if you consume three or more alcoholic beverages daily.
- Do not exceed recommended dosages.
- Products containing aspartame and/or phenylalanine (usually chewable tablets) should not be given to persons with phenylketonuria.

Salicylates (Aspirin and Magnesium Salicylate) and Other NSAIDs (Ibuprofen and Naproxen)

- Do not take salicylates or nonsalicylate NSAIDs during the last 3 months of pregnancy unless a primary care provider is supervising such use. Unsupervised use of this medication could harm the unborn child or cause complications during delivery.
- Do not give aspirin or products that contain aspirin to children and teenagers who have or are recovering from chickenpox or influenza-like symptoms. To avoid the risk of Reye syndrome, a rare but potentially fatal condition, use acetaminophen for pain relief.
- Do not take aspirin or other NSAIDs if you are allergic to aspirin or have asthma and nasal polyps. Take acetaminophen instead.
- Do not take aspirin or other NSAIDs if you have stomach problems or ulcers, liver disease, kidney disease, or heart failure.
- Do not take NSAIDs if you have or are at high risk for heart disease or stroke unless the use is supervised by a health care provider.
- Do not take aspirin if you have gout, diabetes mellitus, or arthritis unless the use is supervised by a health care provider.
- Do not take salicylates or other NSAIDs if you are taking anticoagulants.
- Do not take magnesium salicylate if you have kidney disease.
- Do not give naproxen to a child younger than 12 years.

When to Seek Medical Attention

- Stop taking salicylates or other NSAIDs and seek medical attention if any of the following signs and symptoms are noted:
 - Headache, dizziness, ringing in the ears, difficulty in hearing, dimness of vision, mental confusion, lassitude, drowsiness, sweating, thirst, hyperventilation, nausea, vomiting, or occasional diarrhea. These signs and symptoms indicate mild salicylate toxicity.
 - Dizziness, nausea and mild stomach pain, constipation, ringing in the ears, or swelling in the feet or legs. These signs and symptoms are common adverse effects of salicylates and other NSAIDs.
 - Rash or hives, or red, peeling skin; swelling in the face or around the eyes; wheezing or trouble breathing; bloody or cloudy urine; unexplained bruising and bleeding; or signs of stomach bleeding such as bloody or black tarry stools, severe stomach pain, or bloody vomit (see the box “A Word About NSAIDs and Stomach Bleeding”). These signs and symptoms warrant immediate medical attention.

Acetaminophen

- To avoid possible damage to the liver, do not take more than 4 g of acetaminophen a day (total dose from all nonprescription and prescription single-ingredient or combination products containing acetaminophen).
- Do not drink alcohol while taking this medication.
- Follow dosage instructions for acetaminophen carefully if you have glucose-6-phosphate dehydrogenase deficiency.

When to Seek Medical Attention

- Stop taking acetaminophen and seek medical attention if you develop nausea, vomiting, drowsiness, confusion, or abdominal pain.

Key: NSAID = Nonsteroidal anti-inflammatory drug.

Key Points for Headache

- Most tension-type, migraine, and sinus headaches are amenable to treatment with nonprescription medications.
- Patients with signs and symptoms suggestive of secondary headaches (except for minor sinus headache) or of undiagnosed migraine headaches should be referred for medical evaluation.
- Many patients with frequent headaches may experience improvement after identifying and modifying environmental, behavioral, nutritional, or other triggers for their headaches.
- The choice of nonprescription analgesic depends on patient preferences, presence of precautionary or contraindicating conditions, concomitant medications, cost, and other factors.
- Pharmacists have been identified as key sources of information on nonprescription analgesics to reduce risk for acetaminophen-induced hepatotoxicity and NSAID-induced GI bleeding, cardiovascular events, and nephrotoxicity.
- Use of nonprescription analgesics for headache should be limited to 3 days per week to prevent medication overuse headache.

Chapter 6: Fever

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Fever is a common reason for visits to pediatricians' offices, with the National Ambulatory Medical Care Survey estimating that 6% of all ambulatory visits to pediatricians are related to fever.¹ Fever also is the leading cause of visits to an emergency department for both male and female patients younger than 15 years.² In 2012, patients with the primary complaint of fever made approximately 10.9 million medical office visits, with a slight preponderance of men.³ Fever is more commonly reported in children than in adults: The rate of reported fevers is 10 per 100 children younger than 5 years, versus 0.5 per 100 adults. Nonetheless, occurrence rates do not seem to differ significantly with respect to gender, race, or geographic area of residence in the United States.⁴

In most cases, fever is self-limited and nonthreatening in presentation; however, fever can cause a great deal of discomfort and occasionally may indicate a serious underlying pathologic condition (e.g., acute infectious process) for which prompt medical evaluation is indicated. The principal reason for treating fever is to alleviate discomfort, but the underlying cause should be identified and appropriate management instituted.

Fever must be distinguished from hyperthermia and hyperpyrexia. Fever is caused by a regulated rise in body temperature, maintained by the hypothalamus, in response to a pyrogen. *Fever* is defined by a body temperature higher than the normal core (oral) temperature of 100°F (37.8°C). It thus signals an increase in the body's thermoregulatory set point.

Hyperthermia, by contrast, represents a malfunctioning of the normal thermoregulatory process at the hypothalamic level caused by excessive heat exposure or production.⁵ Because of their different mechanisms, treatment of fever versus hyperthermia also varies.

Hyperpyrexia is defined by a body temperature greater than 106°F (41.1°C; oral) that typically is associated with mental and physical signs and symptoms. Hyperpyrexia may develop with either fever or hyperthermia.

Pathophysiology of Fever

Core body temperature is controlled by the hypothalamus and regulated by a feedback system involving information transmitted between the thermoregulatory center in the anterior hypothalamus and the thermosensitive neurons in the skin and central nervous system (CNS). Physiologic (e.g., sweating, vasodilation) and behavioral mechanisms regulate body temperature within the normal range. Although skin temperature may fluctuate greatly in response to environmental conditions, the core temperature is maintained within a narrow range.⁶

Normal thermoregulation prevents wide fluctuations in body temperature, with the average oral temperature usually maintained between 97.5°F and 98.9°F (36.4°C and 37.2°C, respectively). Temperature maintained in this range is considered to be the “set point” at which physiologic or behavioral mechanisms are not activated. For practical purposes, the commonly accepted core body temperature is usually 98.6°F (37.0°C; oral).

Pyrogens, either exogenous or endogenous, are fever-producing substances that activate the body's host defenses, resulting in an increase in the set point. Exogenous pyrogens (e.g., those of microbial origin or plant toxins) do not independently increase the hypothalamic temperature set point. These substances stimulate the release of endogenous pyrogens (e.g., immune cytokines), thereby increasing the core temperature. Endogenous pyrogens are products released in response to or from damaged tissue, such as interleukins, interferons, and tumor necrosis factor.^{6–8}

Prostaglandins of the E₂ series (PGE₂) are produced in response to circulating pyrogens and elevate the thermoregulatory set point in the hypothalamus. Within hours, body temperature reaches the new set point, and fever occurs. During the period of upward temperature readjustment, the patient experiences chills, caused by peripheral vasoconstriction and muscle rigidity, to maintain homeostasis.⁶

An increase in body temperature may be idiopathic or the result of a variety of mechanisms, including those associated with infectious and other pathologic processes, systemic response to certain drugs, and vigorous activity.

Most febrile episodes are caused by microbial infections (i.e., due to viruses, bacteria, fungi, yeasts, or protozoa). No basis has been found for differentiating viral from bacterial infections according to the magnitude of the fever or temperature reduction with antipyretic drug therapy. Fever often is less

pronounced in older patients; consequently, infection may not be recognized easily, or early, in this age group if fever is the primary assessment criterion.⁹

Noninfectious pathologic causes of increases in temperature include malignancies, tissue damage (e.g., myocardial infarction, surgery), antigen–antibody reactions, dehydration, heat stroke, CNS inflammation, and metabolic disorders such as hyperthyroidism or gout. Many of these processes may cause hyperthermia, rather than fever, because they interfere with the hypothalamic regulation of temperature.

Drug fever is simply defined as a febrile response to the administration of a medication. Its incidence in ambulatory settings is unknown but among hospitalized patients is approximately 10%¹⁰ (Table 6–1). With drug-induced fever, temperatures usually range from 98.9°F (37.2°C; oral) to as high as 109°F (42.8°C; oral). Drug fever should be suspected in patients without an obvious source of fever; however, this condition often goes unrecognized because of inconsistent signs and symptoms. Failure to discontinue the offending drug may result in substantial morbidity and death.^{11,12}

Table 6–1 Selected Medications That Induce Hyperthermia

Anti-infectives	Antineoplastics	Cardiovascular	CNS Agents	Other Agents
Aminoglycosides	Bleomycin	Epinephrine	Amphetamines	Allopurinol
Amphotericin B	Chlorambucil	Hydralazine	Barbiturates	Atropine
Cephalosporins	Cytarabine	Methyldopa	Benztropine	Azathioprine
Clindamycin	Daunorubicin	Nifedipine	Carbamazepine	Cimetidine
Chloramphenicol	Hydroxyurea	Procainamide	Haloperidol	Corticosteroids
Imipenem	L-Asparaginase	Quinidine	Lithium	Folate
Isoniazid	6-Mercaptopurine	Streptokinase	MAOIs	Inhaled anesthetics
Linezolid	Procarbazine		Nomifensine	Interferon
Macrolides	Streptozocin		Phenytoin	Iodides
Mebendazole			Phenothiazines	Metoclopramide

Anti-infectives	Antineoplastics	Cardiovascular	CNS Agents	Other Agents
Nitrofurantoin			SNRIs	Propylthiouracil
Para-aminosalicylic acid			SSRIs	Prostaglandin E ₂
Penicillins			Sumatriptan	Salicylates
Rifampin			Thioridazine	Tolmetin
Streptomycin			Trifluoperazine	
Sulfonamides			TCA's	
Tetracyclines			Topiramate	
Vancomycin			Zonisamide	

Key: CNS = Central nervous system; MAOIs = monoamine oxidase inhibitors; SNRIs = serotonin-norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants.

Source: References 5, 10, and 12.

Drug fever may be differentiated from other potentially causative disorders by establishing a temporal relationship between the fever and the administration of a medication, as well as by observing a temperature elevation despite clinical improvement with respect to the underlying disorder.

The management of drug fever involves discontinuing all medications temporarily, if feasible, in addition to the suspected medication whenever possible. If the hyperthermia is drug-induced, the patient's temperature generally will decrease within 24–72 hours after the offending agent is withdrawn. After the patient's safety has been secured and the offending medication has been identified and discontinued, each medication may be restarted, one at a time, with careful monitoring for fever recurrence.¹²

Clinical Presentation of Fever

Because clinical manifestations of fever are nonspecific and do not occur in all patients, the specific cause of a fever may be difficult to determine. The most important indicator of fever is an elevated body temperature; therefore, accurate temperature measurement is paramount. Fever is symptomatic of a larger underlying process, whether an infection, an abnormality of metabolism, or a drug-induced syndrome.

Once the presence of fever is established, investigation into the underlying cause is essential. Signs and symptoms that typically accompany fever and cause a great deal of discomfort include headache, diaphoresis, generalized malaise, chills, tachycardia, arthralgia, myalgia, irritability, and anorexia. Most children will tolerate a fever well, so if they continue to be alert, play normally, and stay hydrated, the fever is not a reason for great concern. However, high body temperature dulls intellectual function and causes disorientation and delirium, especially in persons with preexisting dementia, cerebral arteriosclerosis, or alcoholism.

Detection of Fever

The most accurate method of assessing for fever is to use a thermometer properly to measure body temperature. The patient's age and level of physical and emotional stress, the environmental temperature, the time of day, and the anatomic site at which the temperature is measured are important considerations in that each factor can affect the temperature reading obtained.

Core temperature is estimated using various types of thermometers at the rectal, axillary, oral, temporal, or tympanic site. Rectal temperature has long been considered the gold standard measurement; however, its utility has been challenged.¹³ Many patients and caregivers prefer other methods of temperature measurement because of comfort and ease of use. Body temperature should be measured with the same thermometer at the same site over the course of an illness, because the readings from different thermometers or sites may vary ([Table 6–2](#)). Discrepancy among the various sites of temperature measurement is normal and should not be ascribed to

improper measurement technique. On average, a rectal temperature greater than 100.4°F (38.0°C), an oral temperature greater than 99.5°F (37.5°C), an axillary temperature greater than 99°F (37.2°C), a tympanic temperature greater than 100.4°F (38.0°C), or a temporal measurement higher than 100.1°F (37.8°C) is considered elevated.^{14,15} The observed variation in temperatures at the different sites is in accord with a simple concept of temperature measurement familiar to the general public: Add 1 degree to an oral temperature to get a rectal or tympanic equivalent, and subtract 1 degree from an oral temperature for an axillary measurement. Normal body temperature may differ by 1.8°F–2.5°F (1.0°C–1.4°C) from these general criteria. Diurnal rhythms cause body temperature to vary during the day, with higher temperatures typically seen in the late afternoon to early evening.

Table 6–2 Body Temperature Range Based on Anatomic Site/Method of Measurement

Site/Method of Measurement	Normal Range^a	Fever^a
Rectal	97.9°F–100.4°F (36.6°C–38.0°C)	>100.4°F (38.0°C)
Oral	95.9°F–99.5°F (35.5°C–37.5°C)	>99.5°F (37.5°C)
Axillary	94.5°F–99°F (34.7°C–37.2°C)	>99°F (37.2°C)
Tympanic	96.3°F–100.4°F (35.7°C–38.0°C)	>100.4°F (38.0°C)
Temporal	97.9°F–100.1°F (36.6°C–37.8°C)	<i>0–2 months of age:</i> >100.7°F (38.1°C)
		<i>3–47 months of age:</i> >100.3°F (37.9°C)
		<i>>4 years of age:</i> >100.1°F (37.8°C)

^a Conversion formulas: Celsius = 5/9(°F – 32); Fahrenheit = (9/5 × °C) + 32.

Source: References 14 and 15.

Because the U.S. Food and Drug Administration (FDA) regulates thermometers as medical devices, all approved types of thermometers are accurate and reliable, if used appropriately. Today's providers should not recommend mercury-in-glass thermometers for use because of environmental concerns about mercury. Federal and state authorities have lobbied for a ban on mercury thermometers, and 13 states have passed laws that prohibit the manufacture, sale, and distribution of mercury-containing thermometers. In addition, the National Institute of Standards and Technology in conjunction with the Environmental Protection Agency will no longer provide any calibration services for mercury-containing thermometers.^{16,17}

Electronic probe thermometers are available for oral, rectal, and axillary temperature measurements. The probes have an electronic transducer that provides a temperature reading in approximately 10–60 seconds. The oral electronic probes are mostly available as either a pen or a pacifier. The pacifier-shaped electronic thermometer is for oral use only and is recommended for infants who are unable to hold a probe under the tongue. The length of time the pacifier needs to stay in the child's mouth varies depending on the manufacturer but can range from 3 to 8 minutes.^{15,18} The pen-shaped probe may be used in oral, rectal, and axillary sites. Because of their electronic digital temperature displays, electronic thermometers provide quick readings, eliminate the possibility of injury from glass breakage, and are easier to read than traditional glass thermometers. The use of disposable probe covers with electronic thermometers also reduces the need for disinfection between uses. Disinfection protocols are still indicated, however, if the thermometer is being used for multiple patients. A thermometer that is used rectally should never be used subsequently for oral measurement.

Infrared thermometers are available for tympanic artery and temporal artery temperature measurements. These thermometers use infrared technology to detect heat from the arterial blood supply. They must be placed directly over the course of the relevant blood vessel, whether near the temporal artery or the tympanic membrane. Infrared thermometers give a temperature reading in less than 5 seconds and are considered very accurate if used properly. The major problem with infrared thermometers is that the device may not always be placed appropriately, or it may have a dirty lens and consequently may give inaccurate readings. Infrared thermometers are relatively expensive and require batteries, but many families with young children prefer them because of their convenience and noninvasive nature. Newer technology also includes

no-touch infrared thermometers, which offer the advantage of not having to wake a sleeping child to take a temperature.^{15,19}

Color-change thermometers are easy to use, but they are not sufficiently accurate or reliable. With these thermometers, an adhesive strip containing heat-sensitive material changes color in response to different temperature gradients. The strip may be placed anywhere on the skin, preferably the forehead, which shows less variation in temperature compared with other parts of the body. Although this method may detect changes in skin temperature, it does not reliably detect changes in core temperature.

Patient-related factors may preclude the use of a particular type of thermometer. Although a variety of routes for temperature measurement are practicable, rectal temperature measurement historically has been the standard, because the site is not influenced by ambient temperatures, and because this route is appropriate for use in patients of various ages.¹⁴ Oral, tympanic, axillary, and temporal routes are all satisfactory for temperature measurement if the proper procedure is followed.

Table 6–3 describes the proper methods of taking *rectal* temperatures in children and adults. Although the rectal route gives the closest estimate of stable core temperature, its intrusive nature can be very frightening and possibly psychologically harmful to older children. In children younger than 3 months, however, rectal temperature measurement is the preferred method for assessing fever and should be recommended if caregivers are confident they can safely use this technique.¹⁵ Risks associated with taking a rectal temperature include retention of the thermometer, rectal or intestinal perforation, and peritonitis. Rectal temperature measurement is also very time-consuming, and the patient should never be left unattended while the rectal thermometer remains in place; a positional change may cause the thermometer to be expelled or broken. Rectal temperature measurement is relatively contraindicated in patients who are neutropenic, have had recent rectal surgery or injury, or have a pathologic process involving the rectum (e.g., obstructive hemorrhoids, diarrhea). In addition, rectal temperature measurement is slow to detect rapid changes in body temperature because of the large muscle mass and poor blood flow in the surrounding anatomic area.^{14,15,20}

Table 6–3 Guidelines for Rectal Temperature Measurement Using Electronic Thermometers

1. Cover the tip of thermometer with a probe cover.
2. Turn on the thermometer and wait until the device signals that it is ready for use.
3. Apply a water-soluble lubricant or petroleum jelly to tip of thermometer to allow for easy passage through the anal sphincter and to reduce risk of trauma.
4. For infants or young children, place child face down over your lap or face up with legs bent to the chest, separate the buttocks with the thumb and forefinger of one hand, and insert the thermometer gently in the direction of the child's umbilicus with the other hand. For infants, insert the thermometer to the length of the tip only. For young children, insert it no more than 1 inch into the rectum.
5. For adults, have the patient lie on one side with the legs flexed to an approximately 45-degree angle from the abdomen. Insert the tip 0.5–2 inches into the rectum by holding the thermometer 0.5–2 inches away from the tip and inserting it until the finger touches the anus. Have the patient take a deep breath during this process to facilitate proper positioning of the thermometer.
6. Hold the thermometer in place until it beeps and a temperature is displayed.
7. Remove the thermometer and record the displayed temperature.
8. Dispose of probe cover and clean thermometer with an antiseptic such as alcohol or a povidone/iodine solution by wiping away from the stem toward tip. Rinse with cool water.
9. Wipe away any remaining lubricant from the anus.

Table 6–4 summarizes the proper methods of *oral* temperature measurement with electronic thermometers.¹⁵ Of note, use of oral measurement techniques is not acceptable in patients who are mouth-breathing or hyperventilating; have recently had oral surgery; are not fully alert; or are uncooperative, lethargic, or confused. Oral digital probe thermometers may not be appropriate for use in most children younger than 3 years of age owing to the difficulty of maintaining a tight seal around the thermometer and keeping the thermometer under the tongue. Accordingly, in these younger children, use of a pacifier thermometer may be recommended. Pacifier thermometers provide reliable temperature readings compared with rectal measurements; however, in children younger than 3 months, pacifier thermometers are less accurate.^{21,22}

Table 6–4 Guidelines for Oral Temperature Measurement Using Electronic Thermometers

Digital Probe

1. Wait 20–30 minutes after drinking or eating.
2. Place a clean disposable probe cover over tip of thermometer.
3. Turn on the thermometer and wait until it is ready for use.
4. Place tip of thermometer under tongue.
5. Close mouth and breathe through nose.
6. Hold thermometer in place until it beeps and temperature has been recorded (usually after 5–30 seconds).
7. Remove the thermometer from mouth and record the displayed temperature.
8. Remove and dispose of probe cover.

Digital Pacifier Thermometer

1. Wait 20–30 minutes after drinking or eating.
2. Inspect the pacifier for any tears or cracks. Do not use if worn.
3. Press the button to turn on thermometer.
4. Place the pacifier in the child's mouth.
5. Have the child hold pacifier in mouth without moving, if possible, for time specified on packaging of thermometer (2–6 minutes).
6. Remove thermometer after the beep and record displayed temperature.

Source: References 15 and 18.

Table 6–5 describes the proper method of using *tympanic* thermometers, which varies slightly with the age of the patient.¹⁵ Tympanic thermometers have digital readouts, and many can be set to provide either a rectal or an oral temperature equivalent. The tympanic membrane is close to the hypothalamus, and the blood supply to both anatomic areas is at the same temperature, providing an accurate reading of the core body temperature. The thermometer must be positioned in the ear canal properly to ensure that the measured infrared radiation is from the tympanic membrane and not from the ear canal or adjacent areas. In clinical trials, accuracy of tympanic thermometers is lower, with more variable readings, than that for thermometers using rectal and oral routes.^{23,24} Variations in measured tympanic temperatures have been attributed to cerumen impaction, inflammation in the ear canal (e.g., otitis media), age of the patient (and corresponding size of the ear canal), and inappropriate technique.¹⁵ Use of tympanic thermometers is not recommended in infants younger than 6

months, in whom the ear canal is not fully developed, leading to inappropriate technique and inaccurate readings. Although not as reliable as the rectal method in children, if used correctly, tympanic thermometry has been found to be more accurate than axillary or oral thermometry in estimating core temperature.²⁰

Table 6–5 Guidelines for Tympanic Temperature Measurement

1. Place a clean disposable lens cover over ear probe or clean probe per manufacturer directions.
2. Turn on thermometer and wait until it is ready for use.
3. For children *6 months to 1 year*, pull ear straight backward to straighten ear canal. Place ear probe into canal, aiming the tip of the probe toward the patient's eye on that side.
4. For patients *older than 1 year*, pull ear backward and then upward to straighten ear canal. Place the ear probe into canal, aiming the tip of probe toward the patient's eye.
5. Press the button for temperature measurement (which usually appears after only 1–5 seconds).
6. Read and record temperature.
7. Discard lens cover.

Source: Reference 15.

Temporal touch thermometers are placed on the side of the forehead directly over the temporal artery and moved across the forehead (**Table 6–6**). The temporal artery is directly supplied by the hypothalamus and is near the surface of the skin at the side of the head, permitting surface measurement using infrared technology. The temporal thermometer is capable of providing a reading in a few seconds. The rapid, noninvasive nature of this method makes temporal touch a preferred route of temperature measurement for most patients, and the temporal thermometer is significantly more sensitive than the tympanic thermometer for detecting fever in infants.²⁵ Of note, however, temporal temperature measurement still has not shown superiority or greater reliability over the rectal method.²¹ Temporal temperatures may differ from rectal temperatures by $\pm 2.3^{\circ}\text{F}$ (1.3°C).^{22,23} The presence of hair near the temporal area may confound the temperature reading, so hair must be pushed away before a reading is obtained.

Table 6–6 Guidelines for Temporal Artery Temperature Measurement

1. Allow thermometer to acclimatize to the environment for about 30 minutes if the thermometer was moved from a hot room to a cold room or vice versa.
2. Remove protective cap and clean probe per manufacturer directions.
3. Place probe on one side of forehead midway between hairline and eyebrows.
4. Depress button and hold while scanning for the temporal artery temperature.
5. Lightly sweep thermometer across forehead to the hairline on the opposite side of the head. Ensure that probe remains in contact with skin at all times, and hold button down until scanning is completed.
6. If sweat is visible on the forehead, sweep the thermometer as normal, but nestle the thermometer on the neck directly behind the ear lobe before releasing the button.
7. Lift thermometer, release the button, and document the recorded temperature.

Source: References 15 and 19.

No-touch infrared thermometers do not require contact of the device with the body for measurement. Temperature is measured by aiming the thermometer at the center of the patient's forehead. Certain models may also allow use of alternative sites such as the navel and neck, although readings at these sites are less accurate.¹⁵ Although no-touch infrared thermometers are convenient and less invasive, a study of children 1 month to 4 years of age treated in the emergency department found no-touch infrared thermometers to be less accurate and reliable than rectal measurement.²⁶

Axillary temperature measurement is frequently used by caregivers and in ambulatory settings, because it is relatively noninvasive. However, axillary measurement performed with digital thermometers (**Table 6–7**) is not as reliable for detecting fever compared with the oral and rectal methods.^{27,28} Reported large variations in temperatures taken by the axillary method are attributable to inappropriate placement of the thermometer, movement of the arm during measurement leading to a poor seal around the thermometer, and insufficient duration of the measurement period. Axillary temperature should not be taken directly after vigorous activity or bathing because both can affect body temperature temporarily without altering the thermoregulatory set point at the hypothalamus. If a fever is detected with the axillary method, a confirmation reading using another method is recommended.

Table 6–7 Guidelines for Axillary Temperature Measurement Using Electronic Thermometer

1. Place a clean disposable probe cover over tip of thermometer or clean probe per manufacturer directions.
2. Turn on thermometer and wait until it is ready for use.
3. Place tip of thermometer in armpit. Ensure that armpit is clean and dry. Thermometer must be touching skin, not clothing.
4. If taking a child's temperature, hold the child close, if necessary, to secure the thermometer within the armpit.
5. Read and record temperature when thermometer beeps.

Source: Reference 15.

Complications of Fever

The presence of fever is of great concern among caregivers, although in most cases fever typically is self-limiting and serious complications are rare. In one study, 73% of caregivers were “very concerned” about the potential complications of fever, and 88% were “very concerned” when a child’s fever was not reduced by antipyretics. There is less concern about complications of fever now than 20 years ago; however, interviewed caregivers still perceived seizures (32%), brain damage (15%), and death (16%) as the main complications of fever.²⁹ Overall, the major risks associated with fever are rare but may include acute complications such as seizures, dehydration, and change in mental status.

Febrile seizure is defined as a seizure accompanied by fever in infants or children who do not have an intracranial infection, a metabolic disturbance, or an otherwise defined cause.³⁰ Febrile seizures occur in 2%–5% of all children from the ages of 6 months to 5 years, with peak occurrence in the age range of 18–24 months. Risk factors for a first febrile seizure include daycare attendance, developmental delay, a family history of febrile seizure, and a neonatal hospital stay longer than 30 days. The severity of the fever and the rate of temperature increase also appear to be critical determinants in the precipitation of a first febrile seizure.³¹ The most common seizures associated with fever are simple febrile seizures, which are characterized by nonfocal movements, generally less than 15 minutes in duration, with only one episode in a 24-hour period.

Significant neurologic sequelae (e.g., impaired intellectual development, epilepsy) are unlikely after a single pediatric febrile seizure. The risk of recurrence is increased in children who have had multiple febrile seizures, are younger than 1 year at the time of their first seizure, and have a family history of epilepsy. Antipyretics generally are recommended to make the child more comfortable, although they do not reduce the risk of recurrent febrile seizures.^{30,32,33} Prophylaxis against simple febrile seizures with antiepileptic or antipyretic drugs is not recommended by the American Academy of Pediatrics.³⁰

Serious detrimental effects (e.g., dehydration, delirium, seizures, coma, irreversible neurologic or muscle damage) occur more often in patients with hyperpyrexia (temperatures >106.0°F [41.1°C; oral]), which is usually associated with hyperthermia and not fever. Because of the homeostatic mechanisms of the hypothalamus, a core temperature exceeding 106.0°F (41.1°C; oral) in a febrile person is rare. Even body temperature elevations of lesser magnitude, however, may be life-threatening in patients with heart disease or pulmonary dysfunction. Increased risk of complications is recognized in infants and patients with brain tumors or hemorrhage, CNS infections, preexisting neurologic damage, and a decreased ability to dissipate heat in concert with lower tolerance of elevated body temperature. Older patients are at a higher risk for fever-related complications because of their decreased thirst perception and ability to perspire.^{6,34}

Treatment of Fever

Overall treatment of fever should focus on the primary cause, rather than on the temperature reading itself. No correlation exists between the magnitude and pattern of temperature elevation (i.e., persistent, intermittent, recurrent, prolonged) and the principal etiologic disorder or severity of the disease. Consequently, determining the cause of the fever on the sole basis of the temperature reading is difficult.

The decision to treat fever is based on a patient-specific risk-benefit ratio and the desire to improve comfort.³⁵ Fever is not associated with many harmful effects unless the temperature exceeds 106.0°F (41.1°C; oral); most fevers are of short duration and may actually have beneficial effects on host defense mechanisms (e.g., antigen recognition, T-helper lymphocyte function,

leukocyte motility). Certain microbes are thermolabile, and their growth may be impaired by higher-than-normal temperatures. Accordingly, overtreatment of fever for viral and bacterial infections may be detrimental.³⁵ Other arguments against treatment include the generally benign and self-limited course of fever, the delayed identification of the diagnosis, and the untoward effects of antipyretic medications.³⁶

Treatment Goals

The major goal of self-treatment is to alleviate the discomfort of fever, rather than treating to achieve a specific temperature.^{35,37}

General Treatment Approach

Treatment of fever using antipyretics (see [Chapter 5](#), Tables 5–2 and 5–3) is most often indicated for patients with elevated temperatures who have an underlying medical problem such as heart or lung disease or have discomfort.³⁸ Fever may be treated with antipyretic agents as well as nonpharmacologic measures.

Self-care measures, including antipyretics, are appropriate initial therapy, unless the patient has exclusions for self-treatment ([Figure 6–1](#)).^{35,37,39} In all cases, self-care measures should be started while medical evaluation is being sought.

Nonpharmacologic Therapy

Nonpharmacologic therapy consists mainly of adequate fluid intake to prevent dehydration. Sponging or baths have limited utility in the management of fever. Body sponging with tepid water may facilitate heat dissipation, in that only a small temperature gradient between the body and the sponging medium is necessary to achieve an effective antipyretic response. However, sponging is not routinely recommended for patients with a temperature less than 104.0°F (40°C; oral); sponging is usually uncomfortable and often induces shivering, which could raise body temperature further. Bathing with ice water or sponging with hydroalcoholic solutions (e.g., isopropyl or ethyl alcohol) is uncomfortable, dangerous, and not recommended owing to risk of cutaneous absorption. Unlike with acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), sponging does not reduce the hypothalamic set point;

therefore, implementation of this measure, if utilized, should be delayed until 1 hour after an oral antipyretic dose, to permit appropriate reduction of the hypothalamic set point and promote a more sustained temperature-lowering response.⁴⁰

Other nonpharmacologic interventions, regardless of the temperature reading, include wearing lightweight clothing, removing blankets, maintaining a comfortable room temperature of approximately 68.0°F (20.0°C), and drinking sufficient fluid to replenish insensible losses. Because a fever will cause a child to lose fluids more rapidly, sufficient fluid intake is recommended to avoid dehydration. Fluid intake in fever should be increased by at least 30–60 mL (1–2 ounces) of fluids per hour in children and by at least 60–120 mL (3–4 ounces) of fluids per hour in adults, unless fluids are contraindicated. Sports drinks, fruit juice, water, balanced electrolyte replacement products, or ice pops may be offered. Milk should also be offered to children who are still on formula or breastfeeding. Caution should be exercised in recommending fruit juice and sports drinks to patients with diarrhea; drinks with high sugar loads may worsen concurrent diarrhea.³⁸

Pharmacologic Therapy

Antipyretics inhibit PGE₂ synthesis, which decreases the feedback between the thermoregulatory neurons and the hypothalamus, thereby reducing the hypothalamic set point during fever. All antipyretics decrease the production of PGE₂ by inhibiting the cyclooxygenase (COX) enzyme. NSAIDs including aspirin inhibit the COX enzyme in both the peripheral nervous system and CNS, whereas acetaminophen mainly inhibits the COX enzyme in the CNS.⁴¹ Chapter 5 provides an in-depth discussion of the pharmacokinetics, dosing, adverse effect profile, interactions, contraindications, and precautions for nonprescription antipyretic agents.

Acetaminophen typically effects a maximum temperature reduction at 2 hours at usual recommended dosing of 10–15 mg/kg every 4–6 hours, with a maximum of 5 doses daily (see Chapter 5, Tables 5–2 and 5–3). Approximately 80% of children will experience a reduction in their fever with this regimen.³⁵ Adult dosing ranges from 325 mg to 1000 mg every 4–6 hours, up to a maximum of 4000 mg daily. Some providers have recommended loading doses of acetaminophen for the reduction of fever at 30 mg/kg per dose, after a small study found a faster (one-half hour) and more significant (0.9°F [0.5°C])

decrease than that achieved with a traditional dose.⁴² This practice is not recommended, however, because of the lack of any follow-up evidence of benefit, as well as the small size and limitations of the study.

Acetaminophen also is available in rectal suppository form. Although a suppository may be an advantage for parents and caregivers who have problems giving their children oral medications, or for children who are vomiting or are having a febrile seizure, absorption with this dosage form is erratic, and studies on its antipyretic activity have yielded conflicting findings.⁴³

Ibuprofen is the most common NSAID used as an antipyretic; maximum temperature reduction typically is achieved at 2 hours at the recommended dosing of 5–10 mg/kg per dose every 6–8 hours, with a maximum of 4 doses per day (see [Chapter 5](#), Tables 5–2 and 5–3). Of note, ibuprofen is approved for the reduction of fever only in patients older than 6 months, and patients and caregivers should recognize the two different pediatric concentrations of ibuprofen available (100 mg/5 mL and 50 mg/1.25 mL). Adult dosing ranges from 200 to 400 mg every 4–6 hours, up to a maximum of 1200 mg daily.

Although NSAIDs and acetaminophen are safe and effective when taken at low doses for short-duration therapy, they should not be used for more than 3 days to treat fever without medical referral for further evaluation to determine the underlying cause. Common medication errors associated with use of nonprescription antipyretics include overdosing or duplicating therapy, attributed to using multiple products with similar ingredients, and inappropriate dosing for pediatric patients, attributed to mathematical errors in calculating a weight-based dose. A study of dosing by parents demonstrated that 51% of pediatric patients received an inaccurate dose of medication (62% for acetaminophen and 26% for ibuprofen).⁴⁴ Because of these alarming statistics, an important function for pharmacist health care providers is to demonstrate to patients and caregivers proper dosing and measurement of the medications with the measuring device provided. In addition, patients should be educated on the appropriate dosing interval and the avoidance of combining antipyretics with cold and cough products containing either acetaminophen or ibuprofen. Furthermore, owing to safety concerns, FDA issued a guidance statement to companies that manufacture, market, or distribute nonprescription liquid medications regarding the dispensing devices that accompany the drug products. Specifically, FDA

recommends that dosage delivery devices such as cups and syringes be included with all nonprescription liquid medications, marked with clear and appropriate calibrated units, and used only with the accompanying medication.⁴⁵

Pharmacotherapeutic Comparison

Both ibuprofen and acetaminophen are more effective than placebo in reducing fever, with both showing reductions of approximately 1 or 2 degrees within 30 minutes to 1 hour. Clinical trials comparing the antipyretic effects of ibuprofen and acetaminophen in recommended dosages have produced variable results, making conclusions on superiority of one or the other agent difficult. A review of the findings in 14 clinical trials comparing ibuprofen and acetaminophen in febrile children found that ibuprofen was slightly more effective than acetaminophen in reducing fever after a single dose; furthermore, ibuprofen was found to be more effective after 6 hours, thus showing a longer duration of action.⁴⁶ The same review found that multiple-dose studies failed to show any statistically significant clinical difference. The risk of serious adverse effects did not differ between the medications. The investigators concluded that the efficacy and safety of acetaminophen and of ibuprofen are similar at recommended dosages, with slightly more benefit for ibuprofen in time to onset of effect and duration of action and fever reduction; however, more conclusive findings are needed. A meta-analysis of data for both children and adults also concluded that ibuprofen was more efficacious than acetaminophen in the reduction of fever in both adults and children and that both were equally safe.⁴⁷ Although ibuprofen has been studied most frequently, other NSAIDs (e.g., naproxen, aspirin) may also be appropriate as antipyretics in adults.

Alternating different antipyretics in the same regimen has become a widespread practice. A survey of 256 caregivers showed that 67% alternated acetaminophen and ibuprofen, and 81% stated that their primary care provider or pediatrician advised them to do so. Although alternating the antipyretics was recommended, only 61% of caregivers received any type of written instructions on how to dose the medications, and the dosing intervals varied, ranging from 2 to 6 hours.⁴⁸ Despite those practices and clinical trials showing lower temperatures at 4 or more hours with combination therapy, the American Academy of Pediatrics does not recommend alternating antipyretics because of the risk of overdose, medication errors resulting from the

complexity of the regimens, and an increased rate of adverse effects.^{35,44} In addition, only one study actually showed less stress and time missed from day care with alternating therapy.⁴⁹ HCPs should be prepared to provide counseling on the practical application of alternating antipyretics if the patient or caregiver has been instructed to use this regimen by a primary care provider. For example, caregivers should be encouraged to write down the generic name, dose, and time of administration for each medication, to minimize the likelihood of duplicate dosing and adverse effects.

The use of antipyretics immediately after vaccine administration is a widespread practice meant to reduce anticipated discomfort and fever. Two open-label randomized trials found that the administration of acetaminophen was effective in reducing febrile episodes, but it also significantly reduced the antibody response to several vaccines, although all levels achieved were still considered protective.⁵⁰ The clinical significance of these antibody reductions is still unknown; nevertheless, the Advisory Committee on Immunization Practices (ACIP) discourages the use of antipyretics before or at the time of vaccination.⁵¹ Symptomatic postvaccination reactions may still be treated with antipyretics until additional data indicate otherwise.

Product Selection Guidelines

Age is an important consideration in the utilization and/or selection of an antipyretic, particularly for neonates. Parents and caregivers of children younger than 3 months of age should immediately seek medical evaluation for rectal temperatures or their equivalent of 100.4°F (38.0°C) or higher. Children older than 3 months with a rectal temperature or equivalent of 104.0°F (40.0°C) or higher should also be referred. Ibuprofen should be used only in children older than 6 months; because of the risk of Reye's syndrome, children and teenagers who have or are recovering from chicken-pox or influenza-like symptoms should not use aspirin or aspirin-containing products.⁵² (See [Chapter 5](#) for a complete discussion of these products.) Special populations of patients, such as pregnant women and older adults, may require additional consideration in assessing fever and referring their care. Specifically, as previously stated, fever may be blunted in older patients, thereby predisposing them to a greater risk of complications if a more serious underlying disorder goes unrecognized. In addition, pregnant women or patients with uncontrolled high blood pressure, heart failure, renal failure, or an allergy to aspirin should avoid use of NSAIDs, including aspirin-containing products. A

detailed description of additional criteria for the appropriate use of antipyretic agents in special populations is available in [Chapter 5](#).

The choice of an antipyretic depends on the patient, since both are safe and effective. Both acetaminophen and ibuprofen are available in a variety of dosage forms and flavors for both children and adults, including tablets, chewable tablets, suspensions, and even suppositories. Selection of a dosage form can be left to patient preference. Consideration of palatability and the taste of the different ibuprofen and acetaminophen suspensions may improve outcomes and adherence to antipyretic regimens in children. (See [Chapter 11](#) under “Special Populations,” for FDA requirements for dispensing devices included in liquid nonprescription products.) The more favorable dosing frequency for ibuprofen of once every 6–8 hours, versus that for acetaminophen of once every 4–6 hours, may also improve adherence and can be considered in product selection, especially in children who have difficulty taking medicine.

Complementary Therapies

Currently, insufficient evidence exists to recommend any dietary supplement or other complementary therapy to treat fever.

Algorithm: Fever

Figure 6–1 Self-care for fever. Key: CNS = Central nervous system; CV = cardiovascular; D/C = discontinue; HIV = human immunodeficiency virus.

Assessment of Fever: A Case-Based Approach

The first step in assessing a patient with fever-related symptoms is to obtain an objective temperature measurement to confirm the presence of fever and rule out any subjective sense of increased body temperature or an inaccurate thermometer reading. If fever is present, assessment of its severity, the seriousness of the underlying cause, and other associated symptoms is indicated. Children who are capable of providing and understanding

information should be included in any dialogue concerning their care.

Cases 6–1 and 6–2 are examples of the assessment of two different patients presenting with fever.

Case 6–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	A worried mother reports that her son Colin came home today after school complaining of not feeling well. She noticed Colin seemed more tired than usual and did not have much of an appetite. She states that before today, Colin was feeling healthy and well. Colin's mother also noticed that his forehead felt warm. When she took Colin's temperature with a tympanic thermometer, it was 102.4°F.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Colin's mom cannot identify anything that makes his symptoms worse or provides relief.
c. Description of the patient's/caregiver's efforts to relieve the symptoms	Neither Colin nor his mother had tried anything to treat his fever up to this point.
d. Patient's identity	Colin Betts
e. Patient's age, gender, height, and weight	12 years, male, 5 ft 1 in., 95 lb
f. Patient's occupation	Colin attends sixth grade.
g. Patient's dietary habits	Normal diet, but he has decreased appetite today.

Relevant Evaluation Criteria	Scenario/Model Outcome
h. Patient's sleep habits	Normal sleep patterns, but he is more tired today.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Seasonal allergies Loratadine 10 mg by mouth once every morning
j. Allergies	NKDA
k. History of other adverse reactions to medications	None
l. Other (describe) _____	Colin also complains of a dull headache that just started this morning. You retake his temperature in the pharmacy using an oral thermometer, which reads 102.1°F.
Assess	
2. Differentiate the patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Colin is experiencing symptoms associated with a fever. When asked, he denies noticing any additional signs or symptoms, suggestive of a more serious illness, that would warrant immediate medical attention.
3. Identify exclusions for self-treatment (Figure 6-1).	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a primary care provider is required, and share this information with the patient/caregiver	Options include (1) Refer Colin for immediate medical attention. (2) Monitor his symptoms and fever, and recommend nondrug measures only. (3) Recommend a medication alone or in combination with nondrug measures. (4) Take no action.
Plan	

Relevant Evaluation Criteria	Scenario/Model Outcome
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient/caregiver preferences.	Colin has a fever and is experiencing some discomfort. He has no exclusions for self-care at this time (Figure 6-1), so treatment with either acetaminophen or ibuprofen is appropriate. Drug therapy should be used in conjunction with nondrug measures. He should not receive any aspirin-containing medications.
6. Describe the recommended therapeutic approach to the patient/caregiver.	See Table 5-2 in Chapter 5 for recommended doses of acetaminophen or ibuprofen. "If fever persists for longer than 72 hours with or without treatment, Colin should be seen by a primary care provider"
7. Explain to patient/caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Colin has a fever that is causing some discomfort, so minimizing the fever with an antipyretic medication, either acetaminophen or ibuprofen, should help. His pediatrician should be contacted if his fever gets worse or persists for longer than 72 hours or if he complains of other symptoms, such as a stiff neck, severe headache or sore throat, or severe ear pain, or if an unexplained rash or repeated vomiting or diarrhea develops."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient/caregiver.	
a. Appropriate dose and frequency of administration	"You can give Colin regular strength acetaminophen tablets (325 mg per tablet). Give 2 tablets every 4-6 hours while symptoms last. Do not exceed 5 doses per 24 hours."
b. Maximum number of days the therapy should be employed	"Do not give Colin the medication for more than 3 days."
c. Product administration procedures	"If Colin cannot swallow tablets, chewable tablets and liquid are available options. Colin should swallow the tablet completely, followed by drinking a full glass of water."

Relevant Evaluation Criteria	Scenario/Model Outcome
d. Expected time to onset of relief	"A reduction in temperature with some relief of discomfort usually occurs within 1/2 to 1 hour. Maximum reduction is usually seen within 2 hours."
e. Degree of relief that can be reasonably expected	"A 1- or 2-degree reduction in temperature is expected, but complete resolution of symptoms may or may not be achieved, depending on the underlying cause of the fever."
f. Most common adverse effects	"Adverse effects are rare, but gastrointestinal effects such as upset stomach or rash are possible. Colin can take the medication with food if an upset stomach occurs."
g. Adverse effects that warrant medical intervention, should they occur	"Contact your primary care provider if signs of an allergic reaction, such as a rash or trouble breathing, occur after a dose is given."
h. Patient's options in the event that condition worsens or persists	"Contact your primary care provider if the fever persists or symptoms worsen beyond 72 hours."
i. Product storage requirements	"Keep medication in a tightly secured container away from any extreme temperatures and out of reach of children."
j. Specific nondrug measures	"Maintain room temperature at 68°F. Encourage adequate fluid intake and have him dress in lightweight clothing."
Solicit follow-up questions from patient/caregiver.	"I read on my favorite 'Mommy Blog' that I can check Colin for fever by feeling his forehead with my palm, which is a lot easier than using that ear thermometer! Is that ok?"
Answer patient's/caregiver's questions.	"You should not use your hand to measure his temperature. This practice is called tactile temperature measurement, and it will not give an accurate representation of his temperature, since your sense of the warmth of his skin may be affected by your own body temperature. If he does not like the ear thermometer, we have many other options, which I am happy to show you how to use."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Colin's mother in 1-2 days to see if Colin's fever is

Relevant Evaluation Criteria	Scenario/Model Outcome
	responding.

Key: NKDA = No known drug allergies.

Case 6–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Mrs. Martinez approaches the pharmacy counter looking for a medication to treat her child's fever. She says her daughter, Ryann, woke up this morning with a red rash on her tummy, arms, and legs and has not been eating. When taking Ryann's temperature orally for the past 5 days, she had temperature readings of 101.4°F, 101.6°F, 102.1°F, 101.7°F, and 101.5°F. Mrs. Martinez does not want to "bother" Ryann's pediatrician since the medical office is "always so busy."
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Ryann's mother states lukewarm baths seem to temporarily soothe Ryann; however, this has not helped to bring down Ryann's temperature.
c. Description of the patient's/caregiver's efforts to relieve the symptoms	Mrs. Martinez has given Ryann 10 mL (2 teaspoonsful) of Children's Advil liquid (100 mg/5 mL) every 6 hours.

Relevant Evaluation Criteria	Scenario/Model Outcome
d. Patient's identity	Ryann Martinez
e. Patient's age, gender, height, and weight	5 years, female, 42 in., 40 lb
f. Patient's occupation	n/a
g. Patient's dietary habits	Ryann eats 3 meals a day with 2 or 3 snacks in between.
h. Patient's sleep habits	Usually sleeps at least 8–9 hours every night, but during the last few nights, she has been getting only 4–5 hours of sleep and takes 30-minute naps during the day.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Advair Diskus 100/50 mcg 1 inhalation twice a day and ProAir HFA 2 puffs every 4 to 6 hours as needed for mild persistent asthma
j. Allergies	NKDA
k. History of other adverse reactions to medications	None reported
l. Other (describe)	n/a
Assess	
2. Differentiate the patient's signs and symptoms, and correctly identify the patient's primary problem(s).	Ryann has a fever that is concerning because of its duration despite treatment; the recent appearance of a skin rash also is concerning.
3. Identify exclusions for self-treatment (Figure 6-1).	Fever lasting for more than 72 hours and skin rash
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a primary care	Options include (1) Refer Ryann to her pediatrician. (2) Refer Ryann to a hospital emergency department for immediate medical attention.

Relevant Evaluation Criteria	Scenario/Model Outcome
provider is required, and share this information with the patient/caregiver.	(3) Monitor her symptoms and fever, and recommend nondrug measures only. (4) Recommend a medication alone or in combination with nondrug measures. (5) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient/caregiver preferences.	Ryann has exclusions for self-care: (1) persistent fever lasting more than 72 hours and (2) appearance of a skin rash. Ryann's mother should contact her pediatrician immediately to rule out any serious conditions.
6. Describe the recommended therapeutic approach to the patient/caregiver.	"No medication is recommended at this time. Immediate medical referral is indicated."
7. Explain to the patient/caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Ryann has a fever that has persisted longer than 72 hours even after treatment with appropriate medication, and a skin rash that appeared today."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient/caregiver.	
a. Appropriate dose and	None recommended

Relevant Evaluation Criteria	Scenario/Model Outcome
frequency of administration	
b. Patient's options in the event that condition worsens or persists	"If fever worsens or continues without improvement, you should take Ryann to a hospital emergency department after speaking with the pediatrician."
c. Specific nondrug measures	"Maintain a room temperature of 68.0°F, and dress her in lightweight clothing."
Solicit follow-up questions from patient/caregiver.	"Can I try giving Ryann ibuprofen (Advil) liquid and acetaminophen (Tylenol) liquid at alternating times until I can get her to her pediatrician?"
Answer patient's/caregiver's questions.	"Alternating between acetaminophen and ibuprofen has not been proven to help children feel better faster, and it may increase risk of adverse effects. I am concerned Ryann may require additional treatment that is not available over the counter. Please call your pediatrician immediately."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Mrs. Martinez in 1-2 days to ensure that she sought medical care for Ryann.

Key: n/a = Not applicable; NKDA = no known drug allergies.

Patient Counseling for Fever

Although fever is a common presenting symptom, it often is misunderstood and poorly treated. Studies suggest that fever may be incorrectly considered a disease associated with detrimental consequences, is frequently treated inappropriately, and is evaluated improperly.⁵³ Many parents and caregivers have "fever phobia," characterized by heightened anxiety regarding effects of fever and in consequent inappropriate treatment.²⁹

Pharmacists as health care providers are well poised to improve clinical outcomes by educating patients and caregivers about fever and by teaching self-assessment skills (e.g., the proper methods for measuring body temperature using the variety of thermometers available, as well as interpretation of the results). If patients and caregivers are still using mercury-in-glass thermometers, they should be urged to dispose of these devices according to local environmental standards. Patient counseling also should include an explanation of the appropriate nonpharmacologic and pharmacologic treatments for fever and should identify indications for seeking further medical care. Discussions of pharmacologic treatments should highlight methods for safe use of antipyretics and nonpharmacologic therapy. The box “Patient

Education for Fever” provides specific information to include in patient counseling.

Evaluation of Patient Outcomes for Fever

The primary monitoring parameters for febrile patients are temperature and discomfort. In one study, 32% of caregivers stated that they would check a febrile patient’s temperature at least every hour.²⁹ Overaggressive monitoring may result from “fever phobia.” Because fever may actually be of physiologic benefit, the ultimate goal of antipyretic therapy is not to normalize temperature but rather to improve overall comfort and well-being.³⁵ The presence of any associated signs and symptoms (e.g., headache, diaphoresis, generalized malaise, chills, tachycardia, arthralgia, myalgia, irritability, anorexia) should also be monitored daily. Although most patients demonstrate a reduction in temperature after each individual dose of an antipyretic, pharmacologic therapy for fever may take up to 1 day to result in core temperature decrease. If clinical improvement is not obtained or if symptoms worsen over the course of 3 days of self-treatment, regardless of a drop in temperature, a primary care provider should be consulted by either phone or appointment for further evaluation.³⁹ Timeliness of patient follow-up assessment with appropriate medical care is important in identifying a non-self-limiting underlying cause.

Patient Education for Fever

The primary objectives of treating fever are (1) to relieve the discomfort of fever and (2) to prevent complications associated with fever. For most patients, carefully following product instructions and the self-care measures listed here will help to ensure optimal therapeutic outcomes.

Temperature Measurement

- Do not rely on skin contact to detect fever. Take a temperature reading with an appropriate thermometer.
- For children up to 3 months of age, the rectal method of temperature measurement is preferred ([Table 6–3](#)). Use of a tympanic thermometer is not recommended in children younger than 6 months because of the specific size and shape of the infant's ear canal.
- For children ages 6 months to 3 years, the rectal, oral, tympanic, or temporal method may be used if proper technique is followed ([Tables 6–3 through 6–6](#)).
- For patients older than 3 years, the oral, tympanic, or temporal method is appropriate ([Tables 6–4 through 6–6](#)).

Nondrug Measures

- Do not use isopropyl or ethyl alcohol for body sponging. Alcohol poisoning can result from skin absorption or inhalation of aerosols from topically applied alcohol solutions.
- For all levels of fever, wear lightweight clothing, remove blankets, and maintain room temperature at 68°F.
- Unless advised otherwise, drink or provide sufficient fluids to replenish body fluid losses. For children, increase fluid intake by at least 1–2 ounces per hour; for adults, increase intake by at least 2–4 ounces per hour. Sports drinks, fruit juice, a balanced electrolyte formulation, and water all are acceptable.

Nonprescription Medications

- Nonprescription analgesics and antipyretics, specifically acetaminophen and ibuprofen (see [Chapter 5](#), Tables 5–2 and 5–3, for dosages), help in alleviating discomfort associated with fever and reducing the temperature, respectively.
- Nonprescription analgesics and antipyretics typically take 30 minutes to 1 hour to begin to decrease discomfort and lower body temperature.
- Monitor level of discomfort and body temperature using the same thermometer at the same body site 2 or 3 times per day during a febrile illness.
- Use single-entity nonprescription analgesics and antipyretics at low doses for up to 3 days for treatment of fever (see [Chapter 5](#), Tables 5–2 and 5–3 for dosages), in the absence of any exclusions for self-care ([Figure 6–1](#)).
- Avoid alternating antipyretics because of the complexity of the dosing regimens, increased risk of medication errors, and adverse effects.
- Dosing of either ibuprofen or acetaminophen in children should be based on body weight, not age.
- To avoid incorrect dosing, use the measuring device that was provided with the product, such as a syringe, dosing spoon, or medicine cup, for administering liquid medication.
- Patients who are pregnant or have uncontrolled high blood pressure, congestive heart failure, renal failure, or an allergy to aspirin should avoid use of nonsteroidal anti-inflammatory drugs (ibuprofen and naproxen sodium) or aspirin-containing products.
- To avoid the possible risk of Reye’s syndrome, do not use aspirin or aspirin-containing products for fever in children and teenagers who have or are recovering from chickenpox or an influenza-like illness.

When to Seek Medical Attention

- Seek medical attention if fever or discomfort persists or worsens after 3 days of drug treatment.

Key Points for Fever

- Fever is self-limiting and rarely poses severe consequences unless the core temperature is greater than 106.0°F (41.1°C; oral).
- The main treatment goals for fever are to alleviate the associated discomfort and to eliminate the underlying cause.
- Fever should be confirmed only by means of a thermometer, which is an FDA-regulated medical device.
- Patients should be educated on the proper measurement techniques for the selected thermometry method.
- Patients should be referred for further evaluation if the rectal temperature or its equivalent is greater than 104.0°F (40.0°C), they have a history of febrile seizures, they have comorbid conditions compromising their health, or they are younger than 3 months of age with a rectal temperature exceeding 100.4°F (38.0°C) or its equivalent.
- Sponge baths using topical isopropyl or ethyl alcohol to reduce fever should be discouraged.
- Acetaminophen and ibuprofen are both safe and efficacious nonprescription medications that may be used as antipyretics in both adults and children.
- Referral for further medical evaluation is appropriate to detect an underlying cause if self-treatment for 3 days does not successfully reduce fever in a patient older than 2 years and for at least 24 hours in a child younger than 2 years of age.
- Health care providers should counsel patients on the proper use of nonprescription antipyretic agents (including appropriate use of measuring devices), to limit medication errors and adverse effects. For patients for whom concomitant use of alternate antipyretic therapies has been recommended, counseling should emphasize the importance of recording the generic name of each

drug given, the dose, and the time of administration, to avoid any adverse effects.

Chapter 7: Musculoskeletal Injuries and Disorders

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Pain is one of the most common reasons for visits to health care providers, including today's pharmacists. Because pain is a common symptom of disease or injury, affected patients often seek medical attention, although many seek to relieve the pain by self-treating with nonprescription analgesics. In a large number of cases, the pain that prompts efforts at self-treatment arises from the musculoskeletal system. Musculoskeletal pain may be felt in the affected tissue itself or referred from another anatomic source (e.g., hip pain referred from its primary source in the low back).¹

Musculoskeletal pain arises from the muscles, bones, joints, and connective tissue. The development of musculoskeletal pain can be acute, such as with sports injuries (e.g., tendonitis, sprains, strains), or it can stem from exacerbation of a pathologic condition (e.g., osteoarthritis). *Acute* pain is typically defined as pain lasting less than 4 weeks. Subacute pain is that experienced in the period after acute pain, lasting up to 3 months. Pain lasting at least 3 months is considered *chronic* pain, which may arise from degenerative joint disease, osteoarthritis, or chronic tendonitis (e.g., carpal tunnel syndrome).¹

The rate of use of nonprescription systemic and topical analgesics remains high, with more than \$4171 million and \$858 million spent, respectively, per year in the United States on such remedies.² The health care provider's assessment should include appropriate questions to identify the type of pain for which the patient is seeking treatment, to elucidate the nature of the pain complaints. In addition, reasonable recommendations should be presented for either self-treatment or further evaluation.

Musculoskeletal complaints result in a significant number of lost workdays, work limitations, loss of employment, and increased utilization of the health care system. These complaints are believed to be the greatest contributors to the economic burden of chronic pain. The total annual cost of persistent chronic pain for adults in the United States is estimated to be \$560 billion. Approximately 20% of adults report chronic pain.³

Pathophysiology of Musculoskeletal Injuries and Disorders

The musculoskeletal system includes the muscles, tendons, ligaments, cartilage, and bones. Muscles are attached to bones by tendons, and ligaments connect bone to bone. Tendons and ligaments normally have limited ability to stretch and twist. Because of their high tensile strength, tendons and ligaments rarely rupture unless subjected to intense forces. However, they may become damaged when the articulation (joint) is hyperextended or with overuse.

Synovial bursae are fluid-filled sacs located between joint spaces to provide lubrication and cushioning. Cartilage functions as protective pads between bones in joints and in the vertebral column.¹

Skeletal, or striated, muscle is composed of cells (myocytes) in which two constituents (actin and myosin) are primarily responsible for contraction. Muscle contraction also involves several electrolytes within the muscle tissue, including calcium and potassium. Pain receptors are located in skeletal muscle and the overlying fascia, and those receptors can be stimulated as a result of overuse or injury to the muscle or surrounding structures.¹

Somatic pain occurs when pain impulses are transmitted from peripheral nociceptors to the central nervous system (CNS) by nerve fibers. Common sites of origin are muscles, fascia, and bones. Somatic pain is most commonly myofascial (e.g., with muscle strain) or musculoskeletal (e.g., with arthritis).¹

Mechanoreceptors and chemoreceptors mediate muscle pain. These nerve endings are heterogeneous in nature: Only a single chemical can stimulate some endings, whereas a variety of chemical, mechanical, and thermal triggers can stimulate others.¹

Erythema (redness), edema, and hyperalgesia (an exaggerated pain response to minor amounts of noxious stimuli) at the affected site characterize the inflammatory response. The inflammatory response develops through participation of multiple mediators, including histamine, bradykinin, serotonin, leukotrienes, and prostaglandin E.¹

Overexertion or *repeated unaccustomed eccentric muscle contraction* is associated with delayed-onset (8 hours or more) muscle soreness, which can last for days, usually peaking at 24–48 hours. This pain reflects muscle damage that presumably was initiated by force generated in the muscle fibers; pathophysiologic components are thought to include inflammation, acidosis, muscle spasms, and/or microlesions. Prolonged tonic contraction produced by exercise, tension, or poor posture and by improper body mechanics can also produce muscle pain. Overexertion injury is common among people who do not exercise regularly but then begin an exercise regimen at a level of high intensity.

Myalgia, or *muscle pain*, can result from systemic infections (e.g., influenza), chronic disorders (e.g., fibromyalgia, polymyalgia rheumatica), and medication effects (e.g., with some cholesterol-lowering agents such as hydroxymethylglutaryl-coenzyme A [HMG-CoA] reductase inhibitors). Abuse of alcohol may precipitate acute alcoholic myopathy. Bone and muscle pain also may be related to vitamin D deficiency, as in osteomalacia. In these conditions, the pain typically is widespread or bilateral in distribution and is not specifically associated with a recent injury.¹

Strains are a result of an injury to a muscle or a tendon. A strain can be caused by an acute injury, or with prolonged overuse, the pathoanatomic changes can result in a chronic condition. The movements that cause a strain involve twisting or pulling. Tendons can become strained when their stretch capacity is exceeded (e.g., hyperextension injury involving an arm or a leg). The strain injury is caused by eccentric contraction of the muscle fibers while the muscle itself is lengthening. A tear of the muscle or tendon also can occur.⁴

Tendonitis is the inflammation of a tendon, which results from acute injury or from chronic repetitive movements (overuse) of a body part. An example of an overuse injury is carpal tunnel syndrome, a condition characterized by tingling or numbness that initially appears in the thumb, index or middle fingers of the hand caused by repetitive use of the hand and wrist. Tendon sheaths become inflamed, with consequent constriction of the median nerve as it passes through a narrow channel between the wrist bones. Tendonitis can also commonly occur in the Achilles tendon, which connects the calf muscle to the heel.¹

Common terms that describe sports-related tendonitis from overuse include tennis elbow, golfer's elbow, swimmer's shoulder, and jumper's knee. In sports-

related overuse injuries, potential contributing factors for tendonitis include older age, poor technique, improper conditioning, exercise of prolonged intensity or duration, and poorly designed equipment for specific activities (e.g., inadequately cushioned athletic shoes).¹

Finally, certain medications (e.g., fluoroquinolone antimicrobials) are associated with the development of tendonitis or tendon rupture. For these medications, the U.S. Food and Drug Administration (FDA) requires the drug label to carry a boxed warning highlighting the risk of such injury.⁵

Bursitis is a common cause of localized pain, tenderness, and swelling in the affected joint, which are worsened by any movement of adjacent structures. Bursitis generally results from an acute injury to the joint or overrepetitive joint action. When pain is accompanied by a local puncture (as from intra-articular injection), a near-by source of infection, or severe inflammation, an infectious cause should be ruled out before self-treatment can be recommended.

Sprains are the most common problem with ligaments. Sprains are graded as follows: Grade I sprains result from excessive stretching, grade II sprains result from a partial tear, and grade III sprains involve a complete tear of the tissue. Grade II and grade III sprains typically are associated with moderate to severe pain, loss of function of the affected limb, and an inability to bear weight. Tears and ruptures are more common in ligaments than in tendons.⁶ Sprains commonly occur during physical activity. It is estimated that 25,000 ankle sprains occur daily.⁷

Low back pain is one of the most common reasons for which patients see their primary care provider. The National Institute of Arthritis and Musculoskeletal and Skin Disease reports that 25% of people report at least 1 day of back pain in a 3-month period.⁸

Main risk factors for the development of low back pain include sedentary lifestyle (particularly one disrupted by bursts of activity), poor posture, wearing improper shoes, excessive body weight, poor-quality mattress and faulty sleeping posture, and improper technique for lifting heavy objects. Most patients recover within a few days to a few weeks, even without treatment; pain that persists for more than 3 months is classified as chronic low back pain.⁹ Other causes of low back pain include congenital anomalies, osteoarthritis, vertebral fractures and compressions, spinal tuberculosis, and referred pain from diseased kidneys, pancreas, liver, or prostate.¹

Osteoarthritis is characterized by a gradual softening and destruction of the cartilage between bones. Over time, cartilage and bone are destroyed in the joint spaces and then regenerate, with consequent rearrangement of the synovial architecture. Often referred to as “degenerative joint disease,” osteoarthritis is caused by genetic, metabolic, and environmental factors. Heavy physical activity, repetitive movement, and lifting of heavy weights may aggravate this condition, whereas routine moderate exercise (i.e., walking, strengthening, neuromuscular training, aquatic, tai chi) does not and is generally beneficial.^{10,11} Approximately 54 million people older than 18 years of age in the United States have a diagnosis of various types of arthritis; by 2040, that number is expected to increase to 78 million.¹²

Clinical Presentation of Musculoskeletal Injuries and Disorders

Table 7–1 lists many of the presenting signs and symptoms of musculoskeletal disorders and other differentiating factors. Pain is a common symptom among all of these disorders.

Table 7–1 Comparison of Musculoskeletal Disorders					
Myalgia	Tendonitis	Bursitis	Sprain	Strain	Osteoarthritis
Location Muscles of the body	Tendon locations around joint areas	Inflammation of the bursae within joints; common locations include knee, shoulder, big toe	Stretching or tearing of a ligament within a joint	Hyperextension of a joint that results in overstretching or tearing the muscle or tendon	Weight-bearing joints, knees, hips, low back, hands
Signs Possible swelling (rare)	Warmth, swelling, erythema	Warmth, edema, erythema, and possible crepitus	Swelling, bruising	Swelling, bruising	Noninflammatory joints, narrowing of joint space, restructuring of bone and cartilage (resulting in joint deformities), possible joint

Myalgia	Tendonitis	Bursitis	Sprain	Strain	Osteoarthritis
					swelling
Symptoms Dull, constant ache (sharp pain relatively rare); weakness and fatigue of muscles also common	Mild-severe pain generally occurring after use; loss of range of motion	Constant pain that worsens with movement or application of external pressure over the joint	Initial severe pain followed by pain, particularly with joint use; tenderness; reduction in joint stability and function	Initial severe pain with continued pain upon movement and at rest; muscle weakness; loss of some function	Dull joint pain relieved by rest; joint stiffness <20-30 minutes; localized symptoms to joint; crepitus
Onset Varies depending on cause (e.g., trauma = acute, but drug-induced = insidious)	Often gradual, but can develop suddenly	Acute with injury; recurs with precipitant use of joint	Acute with injury	Acute with injury	Insidious development over years
Modifying Factors Elimination of cause; use of stretching, rest, heat, topical analgesics, systemic analgesics	Elimination of cause; use of stretching, rest, ice, topical analgesics, systemic analgesics	Joint rest; immobilization; topical analgesics; systemic analgesics	RICE; stretching; use of protective wraps (e.g., ankle tape, knee brace, cane); topical analgesics; systemic analgesics	RICE; stretching; use of protective wraps; topical analgesics; systemic analgesics	Continuous exercise (light-moderate activity); weight loss, heat, analgesic medication; topical pain relievers

Key: RICE = Rest, *ice*, compression, elevation ([Table 7-2](#)).

Source: References 1,4, and 11

In addition to the pain induced by a sprain, impairment of joint function of variable degree will be present. If an apparent sprain is associated with noticeably limited joint function, the injury is most likely to be a grade II or grade III sprain, necessitating proper workup to rule out a fracture or tear. If the affected joint is visibly deformed, emergency medical assistance is warranted.⁴

Patients with carpal tunnel syndrome often describe a diminished ability to feel heat or cold; a sense that the affected hand is swollen, despite the absence of visible change; a weakness in the hand that may affect performance of fine motor movements (e.g., buttoning a shirt); and a tendency to drop things. Symptoms persist during sleep and even when the hand is not being used, a characteristic that can be used to distinguish this disorder from others.

The pain of osteoarthritis does not correlate directly with the degree of joint damage. Pain is often referred, and proximal muscles can be involved if a person with osteoarthritis guards the affected joint by changing the gait to reduce discomfort. Low back pain can also be neuropathic in nature, involving the sciatic nerve, with sharp referred pain in one or both legs. Low back pain can often limit the patient's ability to bend, move, sit, or walk.^{1,8}

Complications of untreated pain-inducing injuries include further tissue damage and (in advanced arthritis) bone and cartilage remodeling. Pain is associated with significant limitations, including a reduction in ability to perform activities of daily living (ADLs), disability, loss of work time, and physical impairments (e.g., insomnia).

Treatment of Musculoskeletal Injuries and Disorders

Acute pain is the body's alarm system; it signals injury by trauma, disease, muscle spasms, or inflammation. Chronic pain, conversely, may or may not be indicative of injury and requires assessment by a primary care provider before treatment is initiated.

Treatment Goals

Treatment of the patient with musculoskeletal complaints encompasses many different goals, the most important of which are (1) decreasing the subjective intensity (severity) of pain; (2) decreasing the duration of pain, when possible; (3) restoring function of the affected area; (4) preventing reinjury and disability (i.e., improving capacity for ADLs); and (5) preventing acute pain from becoming chronic persistent pain.

General Treatment Approach

Patients with musculoskeletal injuries present with common symptoms (especially pain and swelling of the affected area) and generally can use similar self-treatment approaches. Nonpharmacologic therapy consisting of rest, ice, compression, and elevation (RICE), with or without nonprescription oral analgesics and/or topical analgesics, during the first 1–3 days after injury is helpful.⁴ The health care provider should carefully screen the patient for warning signs and symptoms that preclude self-treatment to ensure that the patient receives appropriate care. The algorithm in [Figure 7–1](#) presents a stepwise approach to self-management of pain for patients who have none of the listed exclusions for self-care.

Management of acute back pain can include the use of nonprescription oral or topical analgesics and nonpharmacologic treatments, including the use of heat.¹³ Patients with subacute or chronic low back pain require medical evaluation before they initiate self-treatment, in view of the prolonged duration of symptoms.

Pain associated with osteoarthritis is approved for self-treatment after an initial medical diagnosis. The general treatment approach includes appropriate lifestyle changes (incorporating weight loss, educational, behavioral, psychosocial, and physical interventions) and use of an oral or topical analgesic (e.g., topical NSAID), which may be a nonprescription medication.¹⁰

Nonpharmacologic Therapy

Injury from playing sports or exercising can be prevented by warming up and stretching muscles before physical activity, ensuring proper hydration, and wearing appropriate footwear. For muscle cramps, stretching and massaging

the affected area followed by immediate rest will loosen the muscle. Appropriate hydration is important, and plain water, sports drinks, or enhanced waters with electrolytes may be used based on patient preference.

RICE therapy promotes healing and helps reduce swelling and inflammation associated with muscle and joint injuries (Table 7–2). Ice should not be applied for more than 15–20 minutes because excessive icing causes considerable vasoconstriction and reduces vascular clearance of inflammatory mediators from the damaged area. Thermal therapies also can be recommended for patients with osteoarthritis experiencing pain and/or swelling.¹⁰ Both cold and heat, at temperatures outside the skin’s threshold for tolerance, can be damaging and can result in blistering or burning; with both types of therapies, therefore, direct application of the medium to the skin is contraindicated.

Table 7–2 Guidelines for RICE Therapy

- *Rest:* Rest the injured area and continue until pain is reduced (generally 1 or 2 days). Slings, splints, or crutches can be used if necessary.
- *Ice:* As soon as possible, apply ice to the injured area in 15- to 20-minute increments, at least 3 or 4 times a day. Continue the ice pack therapy until swelling subsides (usually 1–3 days, depending on the severity of injury).
- *Compression:* Apply compression to the injured area with an elastic support or an elasticized bandage, as follows:
 - Choose the appropriate-size bandage for the injured body part. If preferred, a product specifically designed for the injured body part can be purchased.
 - If ice is also being applied to the injured area, soak the bandage in water to aid the transfer of cold.
 - Wrap the injured area by overlapping the previous layer of bandage by approximately one-third to one-half its width.
 - Wrap the point most distal from the injury (e.g., if the ankle is injured, begin wrapping just above the toes).
 - Decrease the tightness of the bandage as you continue to wrap. If the bandage feels tight or uncomfortable, or if circulation is impaired, remove the compression bandage and rewrap it. Cold toes or swollen fingers indicate that the bandage is too tight.
 - After removal, wash the used bandage in lukewarm, soapy water; do not scrub it. Rinse the bandage thoroughly and allow to air dry on a flat surface.
 - Roll up the bandage to prevent wrinkles, and store it in a cool, dry place. Do not iron the bandage to remove wrinkles.
- *Elevation:* Elevate the limb or body part with the injured area at or above the level of the heart, to decrease swelling and relieve pain.

Key: RICE = Rest, ice, compression, elevation. Source: Reference 4.

Heat therapy is an alternative for patients in whom pain of a noninflammatory nature develops and may relieve with stiffness. It has been studied in the treatment of acute low back pain with favorable effects.¹³ In addition, some osteoarthritis guidelines recommend heat as an adjunct nonpharmacologic therapy.^{14–16} The American College of Rheumatology (ACR) and Arthritis Foundation (AF) osteoarthritis guidelines conditionally recommend thermotherapy; the recommendation is based on the short-term benefits of thermotherapy and the difficulty in assessing therapeutic benefit from the literature because of the variety of methods used to deliver heat.¹⁰ Although its mechanism of action is not fully understood, heat may alleviate pain by increasing blood flow, reducing muscle spasm, and relieving stiffness. Heat should be applied for 15–20 minutes, 3 or 4 times a day. Heat should not be applied to inflamed areas because it can intensify vasodilation and exacerbate vascular leakage.

Heat can be applied to the affected area in the form of a warm wet compress, heating pad, or hot water bottle. Ease of use favors newer, heat-generating adhesive and wrap products (e.g., ThermaCare, Precise, various generic brands), which can be worn on the affected area up to 8 hours (up to 12 hours for some products). The products come in various shapes to accommodate different anatomic areas, including back, hip, neck, knee, wrist and hand, shoulder, elbow, and lower abdomen.

The adhesive products should be applied on dry skin that is free of lotion. In a few exceptions, certain products carry unique directions for use (e.g., ThermaCare menstrual product, BodiHeat), such as placing the adhesive side on the undergarment or clothing.

Heating devices should not be used on areas of broken skin or areas with decreased sensation, a practice that can lead to a skin burn. Specifically, ThermaCare heat-generating products should not be placed on the back of the knee or inside the bend of the arm.¹⁷

Although not generally associated with many adverse effects, heat-generating

patches can cause skin irritation or even burns. Patients should be advised to remove the patch immediately if they experience any pain or discomfort, itching, or burning. Heat wraps should be worn over a towel or layer of clothing in patients older than 55 years; heat wraps should not be used during sleep.¹⁷

Limited scientific information is available regarding contrast therapy (alternating heat and ice) to aid in sports injury recovery. Anecdotally, some patients report relief. One study evaluated heat and contrast therapy in the subacute stage of ankle sprain injuries. In the immediate period after applying thermotherapy, heat reduced pain better than contrast therapy. After three days of continuous use, contrast therapy was found to reduce swelling. Insufficient scientific evidence is available in the literature to justify recommendation of this practice; however, the patient may consider use of contrast therapy if it brings relief.⁶

Transcutaneous electrical nerve stimulation (TENS) therapy is used widely by various practitioners (e.g., physicians, physical therapists, chiropractors) in the treatment of pain. FDA has approved TENS therapy for nonprescription use. The TENS device is a class II medical device for the relief of pain associated with sore, aching muscles; joint pain; or chronic intractable pain.¹⁸ Pain relief is thought to come from two mechanisms: alteration of pain transmission and an increase in the production of natural endorphins. A TENS device typically is used for an interval of 15–30 minutes up to 3 times daily. The electrode pads can be placed on various areas of the body for pain relief (e.g., back, legs, ankles, arms, shoulders), but placement is product-dependent. Because of safety concerns, patients should avoid placing the electrodes on the throat, chest, head, or over the carotid arteries. The electrodes also should not be placed on open wounds, rashes, inflamed skin, cancerous lesions, or areas of skin with altered sensation, or over areas treated with topical analgesics. Patients with internal or attached medical devices (e.g., pacemakers, defibrillators, electrocardiographic monitors, respirators), pregnant women, and pediatric populations should avoid using nonprescription TENS devices.^{19,20} The directions for proper and safe use of these devices are product-specific, so a review of the directions with the patient is indicated. The 2019 ACR/AF guidelines strongly recommend against the use of TENS in osteoarthritis of the knee and hip.¹⁰

Historically, some patients prefer to use magnesium sulfate (Epsom salt) solution applied to areas of minor sprains and bruises, for a nonpharmacologic

treatment for relief of discomfort. However, scientific evidence to support claims of effectiveness in the general population is lacking. For this self-treatment modality, the magnesium sulfate is dissolved in warm water for soaking the affected part in a bath or for application on wet bandages for an average of 20 minutes.

Heat, massage, acupuncture, and spinal manipulation are nonpharmacologic therapies recommended to treat acute or subacute low back pain. Patients with chronic low back pain should consider nonpharmacologic measures as first-line treatment. Recommendations include exercise; multidisciplinary rehabilitation; acupuncture; psychological therapies (e.g., mindfulness-based stress reduction, progressive relaxation, cognitive behavioral therapy, electromyography biofeedback, operant therapy); tai chi; yoga; motor control exercise (i.e., focus on strengthening the muscles that support the spine and improving coordination); low-level laser treatments using noninvasive infrared beams as light therapy; and spinal manipulation by a licensed provider (e.g. chiropractor, physical therapist).⁹

Pharmacologic Therapy

Systemic Analgesics

Acetaminophen, aspirin, and non-aspirin nonsteroidal antiinflammatory drugs (NSAIDs), such as ibuprofen, naproxen, and magnesium salicylate tetrahydrate, are commonly used nonprescription analgesics; they are often used in the initial treatment of musculoskeletal injuries. Systemic analgesic therapy for selfcare should be limited to 10 days,²¹ and patients should seek appropriate medical care if the condition continues beyond this period or worsens during the course of treatment. (See [Chapter 5](#) for dosages, safety, and properties of nonprescription systemic analgesics.)

The impact of systemic NSAIDs on muscle recovery after an acute injury has been debated and was evaluated in a recent study. A number of mechanisms have been hypothesized, including the possibility of delayed muscle healing secondary to impaired protein synthesis and cell regeneration. A systematic review and meta-analysis reported that use of NSAIDs, for 14 days or less, after an acute muscle injury conferred a small to moderate benefit in reducing soreness and lowering blood creatine kinase levels. A beneficial effect on strength was observed as well. The study authors noted on data analysis that

NSAIDs seemed to work better with lower body than with upper body injuries and recommended additional research on this topic.²²

For the treatment of osteoarthritis of the hip and knee, acetaminophen has been recommended historically by some organizations for first-line therapy, despite data suggesting that NSAIDs provide slightly better pain relief.²³ A meta-analysis demonstrated a significant effect of NSAIDs and acetaminophen for reducing pain and improving function. However, naproxen was found to be most likely to improve pain control and function in patients with osteoarthritis of the knee.²⁴ In reference to systemic agents, the 2019 ACR/AF guidelines strongly recommend oral NSAIDs and conditionally recommend acetaminophen for patients with knee, hip, and/or hand osteoarthritis.¹⁰ The Osteoarthritis Research Society International (OARSI) 2019 guidelines did not recommend acetaminophen as oral therapy for any type of osteoarthritis.¹⁵

Chronic use of NSAIDs leads to more severe and prevalent adverse effects (e.g., nephropathy, gastrointestinal ulcerations and bleeding, increased risk for cardiac events). According to the OARSI guidelines, a proton pump inhibitor should be considered for gastrointestinal protection if the patient is high risk or if a systemic nonselective NSAID will be used chronically for the management of osteoarthritis.¹⁵ (See [Chapter 13](#) for further information on risks of long-term use of proton pump inhibitors.) The ACR/AF guidelines strongly recommend oral NSAIDs for knee, hip, and hand osteoarthritis. In addition, they also strongly recommend topical NSAIDs for knee arthritis and conditionally recommend them for hand arthritis. The updated guidelines recommend that, when practical, topical NSAIDs be considered prior to the use of systemic NSAIDs to reduce systemic exposure in all age groups.¹⁰

A randomized clinical trial compared the effect of opioid versus nonopioid medications on pain-related function and pain intensity over 12 months. The trial utilized acetaminophen and prescription doses of NSAIDs as first-line therapeutic options; however, the nonopioid group did have access to tramadol, which could be a potential confounder in this study. Over the course of the study, pain intensity was statistically lower in the nonopioid group. There was no difference between the opioid and nonopioid treatment groups in improvement of pain-related function.²⁵

The American College of Physicians (ACP) published guidelines regarding the management of acute, subacute, and chronic back pain.⁹ Among nonprescription medications recommended by a health care provider for the

treatment of acute back pain, acetaminophen is no longer considered a first-line agent. A patient with chronic low back pain should consider nonpharmacologic measures as first-line treatment. In studies including a large randomized, placebo-controlled trial, acetaminophen was no different than placebo in addressing acute low back pain intensity and function.¹³ If the patient has no contraindications to use of NSAIDs, an agent of this group should be recommended over acetaminophen and is considered first-line pharmacologic therapy. Moderate-quality evidence showed that NSAIDs provided some reduction in pain intensity, and low-quality evidence showed some improvement in function. If adequate pain relief is not achieved with the NSAID, the patient should be referred to his or her primary care provider, who may recommend prescription medications.^{9,13}

Topical Products

Topical analgesics may have local analgesic, anesthetic, antipruritic, and/or counterirritant effects. Nonprescription topical analgesics are approved specifically for the topical treatment of minor to moderate aches and pains of muscles and joints (e.g., simple backache, arthritis pain, strains, bruises, sprains).²⁶ In February 2020, FDA reclassified diclofenac gel 1%, a topical NSAID, as a nonprescription drug through the Rx-to-OTC switch process. This agent is approved for relief of joint pain from osteoarthritis in the hand, wrist, elbow, foot, ankle, and knee.^{27,28} A topical anesthetic, lidocaine, is available as a nonprescription medication marketed for nerve pain. Topical nonprescription agents are recommended as adjuncts to pharmacologic and nonpharmacologic therapy of musculoskeletal injuries and disorders. [Table 7–3](#) lists examples of commercially available products.

Table 7–3 Selected Nonprescription External Analgesic Products	
Trade Name	Primary Ingredient(s)
Menthol-Containing Products	
Aspercreme Heat Pain Relieving Gel	Menthol 10%
Bengay Ultra Strength Pain Relieving Patch	Menthol 5%
Icy Hot No Mess Applicator	Menthol 16%
Mineral Ice	Menthol 2%

Trade Name	Primary Ingredient(s)
Camphor-Containing Products	
JointFlex Arthritis Pain Relieving Cream	Camphor 3.2%
Capsaicin-Containing Products	
Capzasin Arthritis Pain Relief No-Mess Applicator	Capsaicin 0.15%
Capzasin-HP Arthritis Pain Relief Cream	Capsaicin 0.1%
Zostrix Maximum Strength Cream	Capsaicin 0.1%
Histamine Dihydrochloride-Containing Products	
Australian Dream Pain Relieving Arthritis Cream	Histamine dihydrochloride 0.025%
Trolamine Salicylate-Containing Products	
Aspercreme Cream	Trolamine salicylate 10%
Sportscreme Deep Penetrating Pain Relieving Rub Cream	Trolamine salicylate 10%
Lidocaine-Containing Products	
Aspercreme With Lidocaine Maximum Strength	Lidocaine hydrochloride 4%
Lidocare Patch	Lidocaine 4%
Diclofenac-Containing Product	
Voltaren Arthritis Pain Gel	Diclofenac sodium 1%
Combination Products	
Arthritis Hot Cream	Methyl salicylate 15%; menthol 10%
Bengay Ultra Strength Pain Relieving Cream	Methyl salicylate 30%; menthol 10%; camphor 4%
Flexall Plus	Menthol 16%; methyl salicylate 10%; camphor 3.1%
Precise Pain Relieving Cream	Methyl salicylate 30%; menthol 10%
Icy Hot Advanced Relief Cream	Camphor 11%; menthol 16%

Trade Name	Primary Ingredient(s)
Icy Hot Lidocaine Cream	Lidocaine HCl 4%; menthol 1%
Mentholatum Ointment	Camphor 9%; natural menthol 1.3%
Salonpas Pain Relief Patch	Methyl salicylate 10%; menthol 3%
Salonpas DEEP Relieving Gel	Camphor 3.1%; menthol 10%; methyl salicylate 15%
Salonpas Lidocaine Pain Relieving Gel-Patch	Lidocaine 4%
Sloan's Liniment	Turpentine oil 47%; capsaicin 0.025%
Tiger Balm Ultra Strength Pain Relieving Ointment	Camphor 11%; menthol 11%

Topical NSAIDs

In February 2020, topical diclofenac sodium 1% (Voltaren) was reclassified as a nonprescription drug for the temporary relief of arthritis pain in the hand, wrist, elbow, foot, ankle, or knee in adults older than 18 years.²⁸ This agent is applied on the skin directly at the targeted site to provide relief from joint pain. Topical NSAIDs share the same mechanism of action for inhibiting prostaglandins, to reduce pain and inflammation, but they are applied locally to the targeted joint that is experiencing pain from arthritis. When diclofenac is applied according to the prescription package insert recommendations (e.g., 4 g applied 4 times per day to one knee), the amount of the agent that is absorbed systemically is 6%, or 17 times lower than the systemic exposure from oral diclofenac.²⁹ The treatment dosage should be the lowest effective dosage for the shortest duration that is consistent with individual patient treatment goals. Although systemic absorption is significantly lower, some absorption does occur. Widespread application on the body or application of the product over broken skin increases its absorption. The health care provider should educate the patient on using the dosing card to measure the proper dose of diclofenac.

Topical diclofenac is contraindicated in patients who are hypersensitive to diclofenac; who have a history of asthma, urticaria, or other allergic-type reactions with use of aspirin or other NSAIDs; and who have undergone coronary artery bypass surgery.²⁹ All NSAIDs, except aspirin, are known to increase the risk of cardiovascular complications (i.e., heart attack, heart failure,

stroke). Patients on low-dose aspirin therapy for cardiovascular or stroke prevention should consult their health care provider. Additional warnings for gastrointestinal complications and renal and liver toxicity also are indicated, because diclofenac belongs to the NSAID drug class.²⁹ A common side effect includes skin irritation that is usually mild.^{29,30} If a serious skin reaction occurs, patients should discontinue use and contact their health care provider.²⁹ Topical diclofenac may take up to 7 days to work, and patients should stop using the product after 21 days. Patients who do not experience improvement in pain after 7 days should contact their health care provider.²⁷

A 2016 Cochrane review concluded that topical diclofenac is effective in reducing pain for osteoarthritis, but that no evidence is available to support its use in other chronic pain conditions. The review also stated that topical diclofenac provided good pain relief but for only 10% more patients than those using a topical placebo.³⁰ The FDA news release also highlighted that topical diclofenac has not been shown to be effective for strains, sprains, bruises, or sports injuries.²⁷

Counterirritants

Topical counterirritants are applied to the skin to relieve pain. Counterirritation is the paradoxical pain-relieving effect achieved by producing a less severe pain to counter a more intense one. The pain relief results more from nerve stimulation than from suppression of the sensation.^{26,31} When applied to the skin at pain sites, counterirritants produce a mild, local inflammatory reaction, which provides symptomatic relief at the site underlying the skin surface being treated. These induced sensations distract from the deep-seated pain in muscles, joints, and tendons. Pain is only as intense as it is perceived to be, and the perception of other sensations caused by the counterirritant or its application (e.g., massage, warmth, redness) causes the sufferer to disregard the sensation of pain.³¹ On the basis of their topical effects, counterirritants are classified into four groups: rubefacients, those that produce a cooling sensation, those that cause vasodilation, and those that incite irritation without rubefaction ([Table 7–4](#)).

Table 7-4 Classification and Dosage Guidelines for Nonprescription Counterirritant External Analgesics

Group	Ingredient(s)	Concentration (%)	Mechanism of Action	Frequency and Duration of Use
A	Allyl isothiocyanate	0.5-5.0	Rubefacients (increase blood flow)	For all counterirritants: Apply no more than 3-4 times/day, as needed, for up to 7 days
	Ammonia water	1.0-2.5		
	Methyl salicylate	10-60		
	Turpentine oil	6-50		
B	Camphor	3-11	Produce cooling sensation	As in group A
	Menthol	1.25-16.0		
C	Histamine dihydrochloride	0.025-0.1	Cause vasodilation	As in group A
	Methyl nicotinate	0.25-1.0		
D	Capsicum	0.025-0.25	Incite irritation without rubefaction; are as potent as group A ingredients	<i>For acute pain:</i> As in group A
	Capsicum oleoresin	0.025-0.25		<i>For chronic pain:</i> Apply 3-4 times/day for duration of pain (often long-term use with medical supervision).
	Capsaicin	0.025-0.25		

^a Dosages approved for adults and for children 2 years and older.

Source: Reference 26.

All regulations and labeling for topical counterirritants are based on the detailed previous proposed rulemaking documents published in the *Federal Register* in 1979 and 1983.^{26,32} FDA has recognized the ingredients in [Table 7–4](#) Category I (generally recognized as safe and effective ([GRASE]) counterirritants for use in adults and in children 2 years of age and older.³² Of note, for many topical nonprescription analgesic products, the lower age limit is older than 2 years.

Labels for most counterirritants indicate that the product is to be used for “the temporary relief of minor to moderate aches and sprains of muscles and joints.” In addition, the labeling recommended by most of the FDA review panels includes claims for “simple backache, arthritis pain, strains, bruises, and sprains.”³² FDA previously issued a Drug Safety Communication about serious burns caused by nonprescription topical counterirritants. Most of the second- and third-degree burn cases were associated with use of topical counterirritant products with higher concentrations of menthol as the single ingredient or with a combination product containing greater than 3% menthol and 10% methyl salicylate. In many of the case reports, the reactions occurred with only one application, and the resulting injury developed within 24 hours. Additionally, some case reports described burns from products containing capsaicin.³³ FDA recommendations for safe use of nonprescription topical analgesic products are presented in [Table 7–5](#). A feeling of warmth or coolness is normal with topical counterirritant use, but patients should seek medical attention if burning pain or blistering occurs.³³

Table 7–5 FDA Recommendations for Application of Nonprescription Topical Analgesic Products

- If pain, swelling, or blistering of the skin occurs after application of a topical analgesic, the patient should immediately discontinue use of the product and seek medical attention.
- Do not bandage the area tightly where the product has been applied.
- Do not use any heat where the product has been applied.
- Do not apply to wounded, damaged, broken, or irritated skin.
- Do not allow these medications to come in contact with the eyes, inside the nose or mouth, or with the genitals.

Key: FDA = U.S. Food and Drug Administration.

Source: Reference 33.

Table 7–4 provides dosing information for the various counterirritants.

Described next are the commonly used counterirritants currently available in the United States.

METHYL SALICYLATE. Methyl salicylate occurs naturally as wintergreen oil or sweet birch oil; gaultheria oil, teaberry oil, and mountain tea are other names for the compound. Methyl salicylate is usually combined with other ingredients (e.g., menthol and/or camphor).

As a rubefacient, methyl salicylate causes vasodilation of cutaneous vasculature, thereby producing reactive hyperemia. This increase in blood pooling and/or flow is hypothesized to be accompanied by an increase in localized skin temperature, which in turn may exert a counterirritant effect. Because of its rubefacient action, methyl salicylate is responsible for the “hot” action in many topical counterirritant products.³¹

In addition to the mechanisms described previously, topically applied methyl salicylate products inhibit both central and peripheral prostaglandin synthesis. Studies on the rate and extent of percutaneous absorption of various commercially available methyl salicylate preparations show direct tissue penetration rather than redistribution by the systemic blood supply, indicating a localized effect of the topical product.³¹

Localized reactions (e.g., skin irritation, rash) and systemic reactions (e.g., salicylate toxicity) may occur with the use of methyl salicylate. Strong irritation may cause local reactions such as erythema, blistering, neurotoxicity, or thermal hyperalgesia. In addition, heat exposure and exercise after applying methyl salicylate have been associated with a threefold increase in systemic absorption of salicylate, which can lead to increases in adverse systemic reactions.³⁴ **Table 7–5** reviews appropriate precautions to take with use of topical analgesics. Because percutaneous absorption of salicylate can occur,

methyl salicylate should be avoided in children and used with caution in individuals who are sensitive to aspirin. Concomitant use of salicylate-containing topical analgesics and maintenance warfarin therapy has been implicated in prolonging prothrombin time.³¹ Chapter 5 describes other potential drug interactions related to systemically absorbed salicylates.

The 2017 report of the American Association of Poison Control Centers documents 5875 methyl salicylate exposures, 4118 of which are in children 6 years of age and younger. In this age group, just a teaspoon of wintergreen oil can cause death.³⁵ Although an FDA survey found that oral ingestion of methyl salicylate in ointment form caused no deaths and that few cases were associated with severe symptoms, regulations require the use of child-resistant containers for liquid preparations containing concentrations greater than 5%.²⁶

CAMPHOR. Although camphor occurs naturally and is obtained from the camphor tree, approximately three fourths of the camphor used medicinally is prepared synthetically.

In concentrations of 0.1%–3.0%, camphor depresses cutaneous receptors and is used as a topical analgesic, anesthetic, and antipruritic. In concentrations exceeding 3%, particularly when combined with other counterirritant ingredients, camphor stimulates the nerve endings in the skin, thereby inducing relief of pain and discomfort by masking moderate to severe deeper visceral pain, with a milder pain arising from the skin at the level of innervation. When applied vigorously, it produces a rubefacient reaction.

Concentrations higher than those recommended are not more effective and can cause more serious adverse reactions if the preparation is accidentally ingested.³² CNS effects, manifested primarily as tonic-clonic seizures, constitute the major form of toxicity and begin to emerge as early as 10 minutes after ingestion. High doses of camphor can cause nausea, vomiting, colic, headache, dizziness, delirium, convulsion, coma, and death.³⁶ Although nonprescription camphor-containing preparations cannot exceed concentrations of 11%, camphor toxicity continues to occur.³⁶ The American Association of Poison Control Centers documented 9975 camphor exposures, with 8252 of the cases in children 6 years of age and younger.³⁵ Parents should be aware of this potential danger, and patient counseling should emphasize use of modalities that do not contain camphor.

MENTHOL. Menthol is either prepared synthetically or extracted from

peppermint oil (which contains a 30%–50% concentration of menthol). Menthol may be used safely in small quantities as a flavoring agent and has found wide acceptance in candy, chewing gum, cigarettes, cough drops, toothpaste, nasal sprays, and liqueurs. It is also used as a permeability enhancer to increase absorption of other topically administered medications.³⁷

At concentrations less than 1%, menthol depresses cutaneous receptor response (i.e., acts as an anesthetic); at concentrations greater than 1.25%, menthol stimulates cutaneous receptor response (i.e., acts as a counterirritant).³⁷

Studies have led to the identification of heat- and cold-sensitive receptors within sensory neurons called transient receptor potential (TRP) cation channels. Topically applied menthol activates the TRPM8 menthol receptor, triggering the sensation of cold.³⁷ The resultant cold sensation travels along pathways similar to the somatic pain sensations from the affected muscle or joint, which distracts from the sensation of pain. The initial feeling of coolness is soon followed by a sensation of warmth.

Menthol is contraindicated in patients with hypersensitivity or sensitization to the agent (e.g., urticaria, erythema, other cutaneous lesions).³⁷ Treatment should be discontinued if the patient experiences irritation, rash, burning, stinging, swelling, or infection.

METHYL NICOTINATE. Although nicotinic acid is inactive topically, methyl nicotinate readily penetrates the cutaneous barrier. Vasodilation and elevation of skin temperature result from very low concentrations, with higher penetration rates reported for hydrophilic media (i.e., gels). One study showed that indomethacin, ibuprofen, and aspirin significantly depress the skin's vascular response to methyl nicotinate. Because these three drugs suppress prostaglandin biosynthesis, the vasodilator response to methyl nicotinate is thought to be mediated, at least in part, by prostaglandin biosynthesis.³⁸

Generalized vascular dilation can occur when methyl nicotinate passes through the skin into the circulatory system. Consequently, persons who apply methyl nicotinate over large areas may experience a drop in blood pressure, a decrease in pulse rate, and syncope secondary to the generalized vascular dilation.³⁸

CAPSICUM PREPARATIONS. Capsicum preparations—capsaicin and capsicum

oleoresin—are derived from the fruit of various species of pepper plants (in the nightshade family). Capsaicin is the major constituent of hot (chili) peppers. Capsicum oleoresin refers to a concentrated extract, containing capsaicin, which is composed of oil and resin.

When applied to normal skin, capsaicin elicits a transient feeling of warmth through stimulation of the TRPV1 receptor. The mechanism of action is thought to be directly related to capsaicin's effects on the depletion of substance P. This substance is found in slow-conducting, unmyelinated type C neurons that innervate the dermis and epidermis. It is released in the skin in response to endogenous (e.g., stress) and exogenous (e.g., trauma, injury) factors. It appears that pruritic stimuli along with pain impulses are conveyed to central processing centers by type C fibers in the skin, for which capsaicin has selective activity. Local application of capsaicin to the peripheral axon appears to deplete substance P from sensory neurons. The depletion occurs both peripherally and centrally, presumably as the result of impulse initiation. When substance P is released, burning pain occurs, but this effect abates with repeated applications. The diminishing sensation experienced with repeated applications can lead to adherence-related failures; health care providers should educate patients about such effects and the importance of continuing therapy.³⁹

Capsaicin has additional indications beyond those of other counterirritants. Capsaicin is used to reduce the pain—but not the inflammation—of rheumatoid arthritis and osteoarthritis; it is also used in the management of a wide variety of other pain disorders (e.g., postherpetic neuralgia, diabetic neuropathy, back pain).

The optimal dose of capsaicin varies among patients. The efficacy of capsaicin decreases (and local discomfort increases) when capsaicin is applied less often than directed, because the drug's duration of action is 4–6 hours. Pain relief is usually noted within 14 days after therapy has begun, but relief will occasionally be delayed by as much as 4–6 weeks in cases of chronic pain.³⁹

Once topical nonprescription capsaicin has begun to relieve pain, its use must continue regularly 3 or 4 times a day, as directed. If capsaicin treatment is stopped and the pain returns, applications can be resumed. Capsaicin may produce a sensation of burning or stinging pain. As a result of tachyphylaxis, however, this local effect diminishes in intensity with repeated applications, typically within a few days but sometimes after as long as 1–2 weeks.^{39,40} To

reduce the likelihood of capsaicin contact with topically sensitive areas (e.g., mucous membranes), patients should be instructed to use a glove for application and to wash their hands after use.³⁹ If the hands are the site of application, the patient should wait 30 minutes after application and then wash the hands. During use, capsaicin should not come in contact with the eyes or other sensitive areas of the body, because it will cause a burning sensation.³⁹ Capsaicin is available in a roll-on applicator or patch formulation, which may be preferred by some patients for its ease of application. Patients using such formulations should still be instructed to wash their hands after handling the product.

Use in patients with hypersensitivity to capsaicin is contraindicated. The agent should be discontinued temporarily if skin breaks down (i.e., appears weeping and red, with development of small ulcers), and the agent should not be applied to wounds or damaged skin.

In addition to skin reactions, capsaicin has also been associated with a cough, “runny nose,” or sneezing if particles are inhaled.³⁵ Overdose with use of capsaicin has not been reported, but more serious and intense adverse effects are reported with higher concentrations.³⁹

Capsaicin also is available in a prescription patch formulation (Qutenza 8%) approved for the treatment of postherpetic neuralgia.⁴¹

ADDITIONAL COUNTERIRRITANTS. Allyl isothiocyanate, ammonia water, turpentine oil, and histamine dihydrochloride are also classified as Category I counterirritants by FDA, but few counterirritant preparations contain those ingredients. Most products that incorporate them also contain other topical analgesics, making any beneficial actions or adverse effects of the products indistinguishable from those of other ingredients. In addition, very little evidence supports the efficacy of such compounds. Allyl isothiocyanate, ammonia water, and turpentine oil are rubefacients, so they should be expected to have effects similar to those of methyl salicylate. However, histamine dihydrochloride causes vasodilation, by mechanisms similar to those for methyl nicotinate.

PHARMACOTHERAPEUTIC EFFICACY AND RECOMMENDATIONS FOR COUNTERIRRITANTS. Literature regarding the efficacy of counterirritants is conflicting, and current studies are lacking. However, Cochrane reviews evaluating the use of counterirritants in specific conditions and guidelines for

osteoarthritis provide some guidance.

One such review reports that topical rubefacients (those specifically containing salicylates) are not supported by enough evidence to be recommended for use in acute or chronic pain. The reviewers noted that studies in assessing acute pain were highly variable in design and limited in number, with small trial sizes and very-low-quality evidence; however, the data showed a 50% pain reduction in 64% of the patients treated after 1 week (number needed to treat: 3) and a 50% pain reduction in 45% of the patients treated after 2 weeks (number needed to treat: 6).⁴²

In the Strategies for Prescribing Analgesics Comparative Effectiveness (SPACE) randomized clinical trial, step-up therapy included topical analgesics, capsaicin, or lidocaine as part of the protocol. Of interest, the nonopioid group reported significantly less pain intensity, and drop-out rates were significantly less.²⁵

One study evaluated the use of a nonprescription combination methyl salicylate and menthol patch for the treatment of mild to moderate muscle strain; the results showed that pain relief was approximately 40% better in subjects using the 8-hour patch than in the placebo group.⁴³ These patch formulations (Salonpas Pain Relief Patch and Salonpas Arthritis Pain Patch) are the only nonprescription analgesic patches to receive FDA approval for a New Drug Application.

Conflicting recommendations have been noted regarding capsaicin. Another Cochrane review focused on reevaluating low-concentration (<1%) capsaicin products for the treatment of chronic neuropathic pain. In this report, insufficient evidence was available to allow a conclusion about low-dose capsaicin in treating neuropathic pain, but such preparations were deemed unlikely to have any “meaningful effect.”⁴⁰ A 2014 Cochrane review concluded that there was moderate evidence for use of capsaicin to reduce low back pain.⁴⁴

The Osteoarthritis Research Society International (OARSI) guidelines recommend against capsaicin for managing osteoarthritis.¹⁵ The ACR/AF guidelines for the management of osteoarthritis conditionally recommend topical capsaicin as an option for symptom management in the knee. Those guidelines, however, also conditionally recommend against the use of capsaicin in the management of osteoarthritis of the hand. No

recommendations regarding nonprescription topical analgesics in the management of osteoarthritis of the hip are included because the depth of the joint beneath the surface makes it unlikely for the agents to have an effect.¹⁰

Other Topical Analgesics

Trolamine Salicylate

Trolamine salicylate is a Category III (nonGRASE) ingredient (insufficient data are available to establish safety and efficacy). Despite this designation, several nonprescription products contain trolamine salicylate as the primary ingredient ([Table 7-3](#)).

It has been suggested that trolamine salicylate (triethanolamine salicylate) is absorbed through the skin, resulting in synovial fluid salicylate concentrations below those of oral aspirin. The recommended topical dosage of trolamine salicylate for adults and for children 2 years of age and older is a 10%–15% concentration applied to the affected area not more than 3 or 4 times a day, as needed. No recent studies have been published regarding the efficacy of topical trolamine salicylate.

Trolamine salicylate is still available as a nonprescription agent and may be most useful to those patients who do not favor the localized irritation or the scent of Category I counterirritants.

Trolamine salicylate has the same considerations for drug interactions and contraindications as those of other salicylates (see [Chapter 5](#)). During use, the agent should not contact the eyes or mucous membranes.

Topical Anesthetics

Lidocaine has widely been available as a nonprescription medication in primarily skin preparations to relieve pain and itching. It is also used for anorectal pain, as a local or injected topical anesthetic, and the prescription patch is approved for postherpetic neuralgia.⁴⁵ In the management of injuries, its primary role is in neuropathic pain owing to its mechanism of action. This mechanism of action includes inhibiting the conduction of nerve impulses. As with other topical analgesics, the FDA-approved time frame is 7 days of use. Patients allergic to lidocaine or other amide local anesthetics should avoid this group of agents. Lidocaine is classified by FDA as Category I, as an external

analgesic, and is approved in concentrations of 0.5%–4% for nonprescription products. It can be used every 6–8 hours as needed, not to exceed 3 applications in 24 hours. The product should be applied to intact skin.^{26,32} If a localized reaction such as a rash, itching, or skin irritation occurs, the product should be removed and the area should be cleansed.

Combination Products

Four separate chemical and/or pharmacologic groups of counterirritants provide four qualitatively different types of irritation.³² Many marketed preparations aim for at least two such effects when greater potency is desired, provided that each active ingredient is from a different group.

Combining counterirritants with skin protectants is not appropriate: the protectants oppose and may nullify counterirritant effects.

Preparation labels must list the active ingredients, including their concentrations, and must identify them by their officially recognized, established names. In addition, manufacturers voluntarily list ingredients on the label. Many manufacturers of combination products list only some of the active ingredients under the “active” heading, and they list many of the other pharmacologically viable products in the inactive ingredients section (e.g., BenGay Vanishing Scent Gel lists camphor and Aspercreme Heat Pain Relieving Gel lists capsaicin under inactive ingredients). Although the concentrations of inactive ingredients are not listed, they are generally below therapeutically determined amounts and are added for reasons other than pain-relieving effects.²⁶

Product Selection Guidelines

Special Populations

No significant variability in response has been noted for patients of different ages or racial backgrounds.

The minimum age of patients on product labeling, as specified by the manufacturer, varies. Such age limits warrant attention in choosing an appropriate topical preparation. According to the tentative final monograph published in the *Federal Register* in 1983, use of external analgesics, as labeled within the confines of the statement, is to be avoided in children younger than

2 years.³² However, most available products elect to label the minimum age as older than 12 years, and some products (particularly capsaicin and diclofenac products) specify 18 years and older. In making recommendations, health care providers should follow labeling instructions for specific products. These products should be used cautiously or avoided entirely in populations in which patients cannot effectively communicate adverse effects they are experiencing after application of a topical analgesic. Of particular concern is use of such products in young children.

Musculoskeletal complaints are common in pregnancy, but complications may occur; therefore, patients should be evaluated by their primary care provider.⁴⁶ Limited information is available regarding use of nonprescription topical analgesics in pregnancy. (See the Preface for a detailed explanation of the pregnancy data.) The prescription capsaicin package insert for Qutenza states that no well-controlled human studies for the patch formulation have been conducted in pregnant women but that animal studies did not reveal teratogenicity. In addition, although controlled studies in nursing mothers are lacking, capsaicin is known to be excreted in breast milk. According to the prescription insert, the exposure to the child can be reduced by avoiding breastfeeding on the day of treatment.⁴¹ Topical lidocaine, at prescription strength, is suggested to be compatible with use during pregnancy and based on limited human data, probably compatible with breastfeeding.⁴⁷ Use of this drug in pregnancy has not been well studied in humans, but animal studies have not shown harm in doses 6.6 times the human dose.⁴⁸ Camphor, menthol, methyl salicylate, trolamine salicylate, and methyl nicotinate were not previously categorized. On the basis of limited data suggesting low risk for adverse effects in this setting, topical camphor is suggested to be compatible with use during pregnancy, and although human data are lacking, it is listed as probably compatible with breastfeeding.⁴⁹

Definitive recommendations are not available because of the limited—or, in some cases, complete lack of—data that are available on topical analgesic use in pregnancy and lactation. Consideration should be given to the systemic absorption of topical salicylates, particularly in the third trimester. This precaution also applies to topical NSAIDs. Information regarding use of salicylates and NSAIDs in pregnancy can be found in [Chapter 5](#). No information on effects on female and male reproductive potential in general is available for the topical analgesics discussed in this chapter.

Patient Factors

The choice of treatment for acute pain syndromes and chronic conditions such as osteoarthritis is patient dependent. In addition to nonpharmacologic treatment, oral drug therapy is often employed. In such decisions, important considerations include the patient's history (identifying any exclusions for self-treatment), other medications the patient is taking, and any known allergies to medications. Topical analgesics are used as an adjunct or substitute to oral drug therapy. If a counterirritant is selected, an agent with Category I GRASE ingredients should be recommended. Product concentrations are variable; in general, the lowest effective dose should be recommended for the shortest duration needed.

Patient Preferences

Factors that affect product selection include dosage form, ease of use, cost, and even odor of the preparation. Both oral and topical dosage forms are available; topical dosage forms available include solutions, liniments, gels, lotions, ointments, creams, and patches. Oleaginous preparations (ointments and oil-based liniments) have increased absorption compared with solutions, gels, lotions, and creams; however, their use is limited owing to an unpleasant "greasy" feel. The use of patches is becoming more popular because of their simple application and long duration of action. With the exception of patches and solutions, topical products should be rubbed into the skin.

Complementary Therapies

The most common dietary supplement used for osteoarthritis contains glucosamine and chondroitin.⁵⁰ Published data regarding these supplements are conflicting because of variability in population size, trial duration, preparations used (e.g., prescription products that are available only in other countries), and outcomes measured (i.e., quality of life, pain indices, and radiologic changes). Initial results from the 6-month Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT) demonstrated no benefit with mild pain but showed a statistically significant reduction with moderate to severe pain. However, only 22% of patients enrolled in the study were categorized as having moderate to severe pain; accordingly, the GAIT investigators concluded that further studies are needed because of the small population size.⁵⁰ A 2-year follow-up evaluation in patients from the GAIT study showed no clinical

difference in reduction of pain and function and joint space width in comparison with placebo.^{51,52}

Reflecting the popularity of these supplements, additional studies continue to contribute to the body of literature. An observational study examined the structural effect of glucosamine and chondroitin sulfate on cartilage in patients with moderate osteoarthritis of the knee who had proven meniscal damage at baseline. The study outcome was assessed at 6 years. In this specific population, use of the supplement for 2 or more years reduced the amount of cartilage lost. The protective effect on cartilage was not associated with symptomatic improvement.⁵³

In the Multicentre Osteoarthritis interVEntional trial with Sysadua (MOVES) trial, investigators concluded that a combination of glucosamine hydrochloride and chondroitin sulfate, as a European prescription product, was similar in efficacy to celecoxib in reducing pain over a 6-month period in patients with severe painful knee osteoarthritis.⁵⁴ For patients with symptomatic knee degenerative joint disease, one study demonstrated that glucosamine plus chondroitin sulfate was no better than placebo in reducing pain or improving function over 6 months.⁵⁵ A 2015 Cochrane review of data on chondroitin, while acknowledging that it mostly included low-quality trials, found that this supplement reduced pain by 10% at 6 months in comparison with placebo for persons with osteoarthritis.⁵⁶ A 2018 systematic review and meta-analysis of glucosamine sulfate reviewed 47 randomized, controlled trials ranging in duration from 1 to 4 years. Although the authors admitted to uncertainty for all estimates compared with placebo, they ultimately reported symptomatic improvement in chronic pain with slow-acting glucosamine sulfate for patients with osteoarthritis. Of note, however, the evidence for this pain improvement emerged after manipulation of the analyzed data using the mean difference on a scale from 0 to 100 and excluding trials with high bias risk.⁵⁷

The effectiveness of and recommendations for glucosamine are controversial. The ACR/AF guidelines recommend strongly against the use of glucosamine in patients with knee, hip, and/or hand osteoarthritis; however, chondroitin sulfate (in combination products with glucosamine) is conditionally recommended in patients with hand osteoarthritis.¹⁰ The AAOS guidelines do not recommend the use of glucosamine and chondroitin for patients with symptomatic knee osteoarthritis.¹⁶ European guidelines support the use of glucosamine and chondroitin but note that this recommendation is based on

the availability of a prescription product.⁵⁸ Use of these products and other complementary therapies is discussed in greater detail in [Chapter 51](#).

Algorithm: Musculoskeletal Injuries and Disorders

Figure 7–1 Self-care for musculoskeletal injuries and disorders. Key: ADR = Adverse drug reaction; FDA = U.S. Food and Drug Administration; OTC = over-the-counter; PCP = primary care provider; RICE = *rest, ice, compression, elevation*. (Source: Adapted from Self-care of self-limited pain. In: Albrant DH, ed. *The American Pharmaceutical Association Drug Treatment Protocols*. 2nd ed. Washington, DC: American Pharmaceutical Association; 2001:424–425.)

Assessment of Musculoskeletal Injuries and Disorders: A Case-Based Approach

With all musculoskeletal injuries and disorders, the health care provider's initial assessment should include an inventory of all patient medications, especially pain medications, and should note the patient's satisfaction with or preference for past treatments. In addition, the clinical interview should ascertain those aspects of the patient's medical history that relate directly to the origin or treatment of pain.

Before any attempt is made to treat a pain complaint, it is essential to qualify and quantify the pain. Inquiry about the cause, duration, location, and severity of pain, as well as factors that relieve and exacerbate the pain, will help in completing a thorough assessment of this symptom. [Chapter 2](#) outlines effective strategies for obtaining information from patients about specific complaints. Using a pain scale helps to quantify the intensity of the pain. With the numerical pain scale, the patient ranks the present pain on a scale of 0–10, with 0 being no pain and 10 being the worst imaginable pain level. Typically, mild pain is defined as a score of 1–3, moderate pain as 4–6, and severe pain as

7–10 on the numerical pain scale.¹ Initially, pain scores establish a baseline for pain before treatment. In addition, a high pain score can be used to identify patients who would be better served by an appropriate medical evaluation. Pain scores also serve as a metric for assessing therapeutic outcomes. Other scales are available for pain rating in children (e.g., Wong-Baker FACES Pain Scale), adolescents, people who do not speak English, and other special populations.

A chronic painful condition presents a different set of challenges. An observant health care provider should intervene with a patient who regularly purchases nonprescription analgesics. If additional interviewing indicates an inadequately treated pain problem, further workup and referral to a primary care provider are appropriate. Information should be offered regarding the risks of inadequate treatment as well as the overuse of medications.

Cases 7–1 and 7–2 are examples of the assessment of two different patients with a musculoskeletal injury or disorder.

Case 7–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (e.g., nature, onset, duration, severity, associated symptoms)	Patient presents with finger and hand pain. She reports that she jammed her finger into the floor during her volleyball game today. The finger is discolored and crooked. She rates the pain as an 8 on a scale of 0–10.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	She reports that any attempt to move her finger results in more discomfort.
c. Description of the patient's efforts to relieve the symptom(s)	The patient has been icing the hand, with minimal relief.

Relevant Evaluation Criteria	Scenario/Model Outcome
d. Patient's identity	Amanda George
e. Patient's age, gender, height, and weight	15 years, female, 5 ft 1 in., 110 lb
f. Patient's occupation	High school student
g. Patient's dietary habits	She is a vegetarian.
h. Patient's sleep habits	She sleeps 7 hours each night. On weekends, sleeps 10 hours a night.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	History of asthma and allergic rhinitis Loratadine 10 mg once daily, albuterol 1 or 2 inhalations as needed, budesonide 180 mcg inhale twice daily
j. Allergies	None
k. History of other adverse reactions to medications	None
l. Other patient preferences	n/a
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Patient is experiencing severe pain in her finger and hand, which may be severely sprained, have a tendon tear, or be dislocated or broken, based on physical presentation.
3. Identify exclusions for self-treatment (Figure 7-1).	The patient has exclusions for self-care. The pain is severe (score greater than 6 on pain scale) and the finger appears dislocated or broken, so an emergency medical referral would be recommended.
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Implement an emergency medical referral for further assessment and treatment. (2) Recommend self-care with an oral NSAID. (3) Recommend self-care until patient can see a

Relevant Evaluation Criteria	Scenario/Model Outcome
	PCP. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Patient should consult a PCP for further evaluation. Nondrug measures such as ice may continue to be used.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"It would be best to seek emergency medical care because of the severity of the pain and the discoloration in the finger. You may continue to ice the area in 15- to 20-minute increments. Between applications, take the ice off for at least 15-20 minutes. Although this is not providing much pain relief, it is likely helping to keep the swelling down."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"It is best to seek medical care, because additional tests such as an x-ray may be needed to determine if the finger is broken or dislocated."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	Criterion does not apply in this case.
Solicit follow-up questions from the patient or caregiver.	The patient's mother asks: "Can I just buy a finger splint for my daughter?"
Answer the patient's or caregiver's questions.	"No, you should take her for a medical evaluation so that the injury can be assessed."
Follow-up: Monitor and Evaluate	

Relevant Evaluation Criteria	Scenario/Model Outcome
9. Assess patient outcome.	Maintain scheduled contact with the patient or her mother, by email or phone, to monitor for a reduction in her reported pain level using a pain scale.

Key: n/a = Not applicable; NSAID = nonsteroidal anti-inflammatory drug; PCP = primary care provider.

Case 7-2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (e.g., nature, onset, duration, severity, associated symptoms)	Patient presents with a complaint of low back pain that started as a dull ache approximately 3 days ago. She rates her pain now as a 4 on a scale of 0-10.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	She reported sleeping on a couch over the past week while on vacation. The achiness began when she woke up 3 days ago. She reports the discomfort is located in her lower back and she describes the pain as a dull ache. She states it is tolerable but annoying, especially when she needs to work all day.
c. Description of the patient's efforts to relieve the symptom(s)	She started taking 1000 mg acetaminophen 3 times daily for 2 days; she denied obtaining improvement or relief.
d. Patient's identity	Lynda Byrd
e. Patient's age, gender, height, and weight	22 years, female, 5 ft 2 in., 160 lb

Relevant Evaluation Criteria	Scenario/Model Outcome
f. Patient's occupation	Grocery store clerk
g. Patient's dietary habits	She prefers quick, easy meals (frozen meals, drive-through food or other grab-and-go options).
h. Patient's sleep habits She sleeps approximately 8–10 hours each night.	
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	She has a history of allergies and takes cetirizine 10 mg one tablet at bedtime. She uses NuvaRing (etonogestrel/ethinyl estradiol vaginal ring) as prescribed. She takes a Flintstones gummy multivitamin once daily.
j. Allergies	None
k. History of other adverse reactions to medications	None
l. Other (describe) _____	n/a
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Patient is experiencing acute low back pain, which is most likely from improper sleeping posture.
3. Identify exclusions for self-treatment (Figure 7-1).	Patient does not have any exclusions for self-care. If her pain were more severe (score greater than 6 on pain scale) or had lasted longer than 10 days, a medical referral would be recommended.
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer patient to PCP for further assessment and treatment. (2) Continue acetaminophen. (3) Recommend an alternative agent (NSAID such as ibuprofen or naproxen).

Relevant Evaluation Criteria	Scenario/Model Outcome
	(4) Recommend nondrug measures (heat). (5) Recommend a topical analgesic, either a single or a combination product. (6) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Recommend nondrug measures, including heat since this is an acute back stiffness due to poor posture. Encourage proper sleep posture if possible. The patient is a candidate for self-care, so recommend an oral analgesic. The patient does not have any contraindications to an oral NSAID regimen, which is first-line therapy.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"A medication in the NSAID class can be used to help relieve your low back pain, and we can select either naproxen or ibuprofen to take by mouth."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Since acetaminophen is not providing adequate relief and NSAIDs have better evidence for low back pain relief, either naproxen or ibuprofen by mouth can be tried as an alternative treatment to relieve the pain."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
a. Appropriate dose and frequency of administration	"Take naproxen 220 mg by mouth every 8 to 12 hours if needed for pain. Do not exceed 3 doses (660 mg) in a 24-hour period."
b. Maximum number of days the therapy should be employed	"This medication can be used for self-treatment for up to 10 days."

Relevant Evaluation Criteria	Scenario/Model Outcome
c. Product administration procedures	"Take 1 tablet every 8 to 12 hours if needed for pain. For the first dose, you may take 2 tablets within the first hour. Do not exceed 2 tablets in any 8- to 12-hour period. Do not exceed 3 tablets in a 24-hour period. Take with food to minimize stomach upset."
d. Expected time to onset of relief	"You should expect to get some relief from the pain within 60 minutes after taking your first dose."
e. Degree of relief that can be reasonably expected	"The medicine will help reduce the pain, but it may not completely eliminate it."
f. Most common adverse effects	"Most common side effect is some stomach upset, which can be minimized by taking this with food."

Key: NSAID = Nonsteroidal anti-inflammatory drug; PCP = primary care provider.

Patient Counseling for Musculoskeletal Injuries and Disorders

Consultation with the patient should include an explanation of the expected benefit of any recommended medication, the appropriate dose and drug administration schedule, application directions, potential adverse reactions, potential drug–drug or drug–disease interactions, and self-monitoring techniques for assessing response to therapy. Printed materials reinforce verbal information. Many such pamphlets or single-page handouts are available from national professional societies (e.g., www.arthritis.org). These materials offer advice on exercise, diet, and sleep habits, as well as outlining the advantages and disadvantages of pharmacologic therapy.

In acute pain management, early administration of nonprescription analgesics is warranted to prevent escalating pain, with downward tapering of the analgesic doses as pain severity allows. Patients should be assessed for the appropriateness of nonprescription oral analgesic regimens ([Chapter 5](#)).

Patients should be instructed to notify their primary care provider if the pain worsens in quality or severity, or if new acute pain develops. Other sudden, uncharacteristic pain may be a sign of new tissue damage.

The box “Patient Education for Musculoskeletal Injuries and Disorders” lists specific information about oral and topical analgesics, as well as preventive and nondrug measures, to include in patient counseling.

Patient Education for Musculoskeletal Injuries and Disorders

The objectives of self-treatment are (1) to reduce the severity of pain; (2) to reduce the duration of pain, when possible; (3) to restore function to the affected area; (4) to prevent re-injury and disability; and (5) to prevent acute pain from becoming chronic persistent pain. Certain nondrug measures and nonprescription topical analgesics can relieve pain from a sudden and recent muscle, tendon, or ligament injury; an overuse injury (e.g., tendonitis, bursitis, repetitive stress injury); low back pain; or arthritis. For most patients, carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

Preventive Measures

- To prevent muscle or joint strains and sprains, do warm-up and stretching exercises before playing sports or exercising, and wrap injured muscle or joint with protective bandage or tape.
- To prevent repetitive strain, exercise the muscles that are vulnerable to the injury, and use ergonomic controls to adjust posture, stresses, motions, and other damaging physical factors.
- To prevent tendonitis and cramps, do warm-up and stretching exercises before physical activity, drink sufficient fluids, and do not exercise to the point of exhaustion. To help prevent nocturnal leg cramps, raise the foot of the bed. For Achilles tendonitis, wearing better-fitting shoes with heel lifts may help alleviate the symptoms.
- To prevent or reduce the occurrence of low back pain, do exercises

to strengthen the muscles of the low back and abdomen, and use assistive devices (e.g., cane or walker) if needed.

- To prevent or reduce the occurrence of osteoarthritis, avoid a sedentary lifestyle; keep joints active; lose weight, if overweight; and use assistive devices if needed.

Nondrug Measures

- For pain related to muscle or joint injuries, begin treatment with RICE therapy ([Table 7–2](#)).
- For periodic muscle cramps, stretch and massage the affected area immediately; then rest or reduce activity of the muscle to allow it to loosen.
- For stiffness, apply heat to the affected area in the form of a warm wet compress, a heating pad, single-use patch, or a hot water bottle.
- For osteoarthritis, try a combination of nondrug measures, including physical, psychosocial, and mind–body approaches to manage pain.

Nonprescription Medications

- For mild to moderate muscle pain, take a nonprescription oral analgesic for no longer than 10 days²¹ (see [Chapter 5](#) for a listing of nonprescription analgesics), and/or use a topical analgesic for no longer than 7 days³² ([Table 7–4](#) provides recommended dosages of counterirritants).
- Topical NSAIDs should be considered a first-line option for osteoarthritis. If pain relief does not occur with 7 days of use, you should see your health care provider. These medications should not be used longer than 21 days without consulting a health care provider.²⁷
- Do not use topical analgesics if your skin is abraded, sunburned, or otherwise damaged.
- When using counterirritants, especially capsaicin, wash your hands after application and before touching your eyes and mucous membranes, or before handling contact lenses.

- Gently rub a thin layer of topical products into affected muscles or joints until you cannot see the product. Thick application does not make the product work better.
- Do not put a tight bandage or dressing over an area treated with a counterirritant. Do not use heat or warming devices with counterirritants.
- Do not treat a child 2 years of age or younger with counterirritants unless a primary care provider supervises the use. Follow age limits on product labeling.
- If you have asthma and experience worsening of symptoms of wheezing and shortness of breath while you are using a mentholated formulation or an NSAID, stop using it.
- If you are receiving anticoagulation therapy (especially warfarin), do not use products containing salicylates (i.e., methyl salicylate and trolamine salicylate) or topical NSAIDs for a prolonged time without monitoring.
- If a counterirritant or topical analgesic product causes excessive redness and blistering or hives and vomiting, stop using it.

When to Seek Medical Attention

- A feeling of warmth or coolness is normal; however, if burning pain or blistering occurs, seek medical attention.
- If you experience nausea, vomiting, colic, and other unusual symptoms while using a product containing camphor, seek medical care immediately.
- If the pain has been present for more than 10 days or has worsened, consult your primary care provider.²¹
- If the symptoms persist after more than 7 days of treatment with a topical product, or if the pain is constant and can be felt in any position, consult your primary care provider.³²

Key: NSAID = Nonsteroidal anti-inflammatory drug; RICE = rest, *ice*, compression, elevation.

Evaluation of Patient Outcomes for Musculoskeletal Injuries and Disorders

The primary indicator of treatment effectiveness is the patient's perception of pain relief. If the patient reports that the pain is still present or has worsened after 7 days of using topical nonprescription analgesics³² or after 21 days of using a topical nonprescription NSAID,²⁷ referral for further evaluation is indicated. In many instances, the lack of a return visit to the health care center indicates a successful treatment regimen (a follow-up call to the patient in a few days will determine whether the complaint has resolved). However, a patient who returns with signs of continued swelling, pain, or inflammation should be referred for medical evaluation.

Key Points for Musculoskeletal Injuries and Disorders

- Among patients presenting with pain secondary to an injury or a disorder of the musculoskeletal system, self-treatment should be limited to those with mild to moderate pain and no exclusions for self-treatment ([Figure 7-1](#)).
- Self-treatment for acute musculoskeletal injuries should include nondrug therapy, such as RICE. Heat therapy also may provide benefit after symptoms of inflammation have abated.
- Systemic analgesics are valid first-line agents to treat a majority of musculoskeletal injuries and disorders. Acetaminophen is appropriate in noninflammatory diseases, whereas NSAIDs are preferred if inflammation is present. Adverse effects and drug interactions should be considered before therapy is chosen (see [Chapter 5](#)).
- Patient counseling should include the discussion points listed in [Table 7-5](#) to avoid chemical burns with topical nonprescription analgesics.

- Health care providers should monitor the outcome of self-treatment regimens and advise patients who self-treat their acute musculoskeletal injury with a nonprescription topical analgesic or NSAID to seek medical attention if they do not obtain symptomatic improvement after 7 days. Regardless of the selected treatment, patients who experience pain for longer than 10 days, with the exception of osteoarthritis-induced pain, also should be referred. Patients who have used a nonprescription NSAID for more than 21 days should consult their health care provider.

Chapter 8: Vaginal and Vulvovaginal Disorders

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Vaginal infections are common among women, with bacterial vaginosis (BV), vulvovaginal candidiasis (VVC), and trichomoniasis occurring most frequently. Many factors affect the risk of vaginal infections such as changes in the normal flora, vaginal pH, douching, and the number of sex partners. VVC is the primary vaginal infection that can be appropriately self-treated. The availability of nonprescription vaginal pH selftesting devices can reduce the risk of inappropriate treatment with nonprescription products as vaginal pH does not increase in VVC, unlike the elevation that occurs with bacterial vaginosis and trichomoniasis. Nonprescription imidazoles include clotrimazole, miconazole, and tioconazole, which are available as vaginal creams, suppositories, and tablets. The drugs are the first-line options to treat uncomplicated VVC and few differences exist between products. The selection of one product over another is based on patient preference rather than product specifics. The use of complementary therapies such as lactobacillus products may decrease the recurrence of VVC. In addition to VVC, this chapter also reviews atrophic vaginitis and douching. Atrophic vaginitis is an inflammation of the vagina potentially leading to painful intercourse, also known as dyspareunia. Multiple nonprescription vaginal lubricants are available and may be beneficial in reducing the symptoms associated with atrophic vaginitis. Douching is the use of products to mechanically irrigate the vagina and clear away mucus. A common reason for douching is to cleanse the vagina, however, douching may lead to adverse health outcomes including disruption of the normal vaginal flora and pH. More seriously, the practice has been associated with an increased risk of pelvic inflammatory disease. Women should be advised about the possible adverse health effects of douching and that this practice is unnecessary as the vagina is a self-cleansing organ.

Vaginal symptoms are among the most common health concerns of women, either of reproductive age or older. Vaginal symptoms may be experienced by all women, whether sexually active or abstinent, homosexual or heterosexual, and premenopausal or postmenopausal.¹ Approximately 65% of women experiencing vaginal symptoms will have one of three common vaginal infections: bacterial vaginosis (BV), vulvovaginal candidiasis (VVC), and

trichomoniasis.¹ Infections also may be mixed, with more than one causative organism.

In general, vaginal infections are perceived as minor health problems for which patients may consider self-treatment. Women also may self-treat for vaginal signs and symptoms of noninfectious origin, such as vaginal dryness, atrophic vaginitis, and allergic or chemical dermatologic reactions.^{1,2} BV and trichomoniasis, however, have been linked to significant health problems, such as pelvic inflammatory disease (PID), preterm birth, and facilitation of transmission of human immunodeficiency virus (HIV).^{2,3} In view of the frequency of these vaginal infections and the current availability of nonprescription vaginal antifungal products, health care providers need to manage these infections carefully and provide appropriate patient education regarding VVC. It is essential to ensure that patients are making informed self-care decisions by providing them the necessary information and tools to know when and how to self-treat.

The vagina is an elastic fibromuscular tube that extends 8–10 cm from the vulva to the uterus. The upper end of the vagina is closed except for the *cervical os*, the opening to the cervix or neck of the uterus. Anatomically, the vagina lies between the urinary bladder and the rectum. At the lower (vulvar) end of the vagina are the Bartholin glands, which produce secretions in response to sexual stimulation. At puberty, with the influence of estrogen, the vaginal lining changes to stratified squamous epithelium, which contains glycogen. *Lactobacillus* bacteria convert glycogen to lactic acid, which creates an acidic pH of 4–4.5. This acidic pH and the production of hydrogen peroxide by these bacteria in some patients help protect the vagina from infection with other bacteria. With menopause, changes in vaginal flora, especially *Lactobacillus* species, may occur as a consequence of reduced estrogen, as well as increases in vaginal pH, potentially leading to vaginal atrophy.⁴

The mature vagina is colonized by many organisms. *Lactobacillus* species predominate, accounting for more than 95% of the vaginal flora.⁵ Additional bacterial organisms, including *Mobiluncus*, *Gardnerella vaginalis*, *Prevotella*, and *Bacteroides*, are present in small quantities, with *Candida albicans* isolated in the absence of active infection in approximately 20% of women.²

The vaginal ecosystem is affected by the number and types of endogenous organisms, vaginal pH, and glycogen concentration. Hormonal fluctuations during the menstrual cycle, in addition to other factors such as drug therapy,

douching, and number of sex partners, also can influence the vaginal ecosystem.

The healthy vagina is cleansed daily through production of secretions that lubricate the vaginal tract. The normal vaginal discharge of these secretions, termed *leukorrhea*, is odorless, clear or white, and viscous or sticky.⁶ This physiologic leukorrhea should not be associated with irritation, itching, or burning. An increase in vaginal secretions is normal during ovulation, during pregnancy, after menses, and with sexual excitement or emotional flares. Alterations in vaginal secretions also may occur in response to vaginal irritants such as feminine hygiene deodorant products and vaginal douches, as well as presence of barrier contraceptive products or tampons.

Differentiation of Common Vaginal Infections

The clinical manifestations of different vaginal infections may be similar, making diagnosis challenging; the characteristic signs or symptoms that often help differentiate such infections also may be absent ([Table 8–1](#)). Accurately distinguishing VVC from BV and trichomoniasis is important because of the availability of nonprescription vaginal antifungal therapy for VVC.

Table 8–1 Differentiation of Common Vaginal Infections		
Classic Signs and Symptoms ^{1,15}	Differentiating Findings ^{1,3,11,14,15}	Etiology and Epidemiology ^{1,3,13,16}
Bacterial Vaginosis (vaginal pH >4.5)		
Thin (watery), white or gray, sometimes foamy discharge; unpleasant “fishy” odor that increases after sexual intercourse or menses; increased vaginal pH (e.g., with menses)	Vaginal irritation and dysuria are less frequent with BV than with VVC or trichomoniasis. A foul odor is strongly associated with BV; absence of odor rules out BV.	Polymicrobial infection resulting from imbalance in normal vaginal flora, with increases in <i>Gardnerella vaginalis</i> , anaerobes (<i>Mobiluncus</i> and <i>Prevotella</i>), and <i>Mycoplasma hominis</i> and decreases in <i>Lactobacillus</i> species Risk factors: multiple or new sexual partner, use of an IUD, douching, sexual practices, tobacco use, and prior pregnancy Responsible for 30% of vaginal symptoms Predominantly affects sexually active

Classic Signs and Symptoms ^{1,15}	Differentiating Findings ^{1,3,11,14,15}	Etiology and Epidemiology ^{1,3,13,16}
		women but can arise spontaneously regardless of sexual activity
Trichomoniasis (vaginal pH >4.5)		
Frothy, malodorous, yellow-green (or discolored) discharge; pruritus; possible vaginal irritation; dysuria No symptoms initially in ~50% of affected women with approximately 30% developing symptoms in 6 months Most men asymptomatic; serve as reservoirs of the infection	Vaginal pruritus (itching) and possible irritation may occur. Frothy, yellow-green, malodorous discharge more likely to be associated with trichomoniasis	STI caused by <i>Trichomonas vaginalis</i> Risk factors: multiple sex partners, new sexual partner, nonuse of barrier contraceptives, and presence of other STIs Responsible for 15%–20% of vaginal infections
Vulvovaginal Candidiasis (no change in vaginal pH)		
Thick, white (“cottage cheese”) discharge without odor; dysuria; normal pH (see text for detailed information; also referred to as “yeast infection”)	Vaginal itching, irritation, erythema, and absence of malodor increase likelihood of VVC; thick, “cheesy” discharge is strongly predictive of VVC.	Organisms: <i>Candida albicans</i> , <i>Candida glabrata</i> , <i>Candida tropicalis</i> , <i>Candida parapsilosis</i> , and <i>Candida krusei</i> Risk factors: pregnancy, use of medications such as antibiotics and immunosuppressive agents No identifiable cause for most infections Responsible for 20%–25% of vaginal infections

Key: BV = Bacterial vaginosis; IUD = intrauterine device; OC = oral contraceptive; STI = sexually transmitted infection; VVC = vulvovaginal candidiasis.

Given the availability of nonprescription vaginal antifungal products, patients may prefer to self-treat for presumed VVC; this approach, however, may potentially lead to improper therapy.⁷ Women should be encouraged to consult an appropriate health care provider, who can identify optimal measures for self-care.

Many women and health care providers may have trouble identifying VVC on the basis of signs and symptoms alone.^{8,9} The feature most likely to differentiate a *Candida* vaginal infection from BV and trichomoniasis is absence of an offensive odor of the vaginal discharge.⁸

Noninfectious conditions such as irritation or pruritus caused by allergic reactions secondary to douching or exposure to feminine hygiene products, latex, spermicides, or soaps also may add to the confusion of diagnosing vaginal infections.⁸

Inappropriate use of vaginal antifungal products carries several risks, including unnecessary drug use and a delay in effective treatment for an underlying condition. Product labels advise patients to seek help for persistent symptoms. If these guidelines are followed, the delay in treatment from misdiagnosis will likely present few serious consequences.

One method to assist patients in appropriate self-care management is the use of vaginal pH self-testing devices to identify elevations in pH, indicating a need for medical evaluation. One study compared the results obtained by a patient's use of a pH self-testing device with their providers' vaginal pH testing to ensure ease and accuracy of use of the device by the patient. Nearly 85% of the patients obtained pH results similar to those obtained by the providers. This outcome supports the use of such tools as an important screening device to assist in self-diagnosis or to encourage further medical evaluation.¹⁰ The use of vaginal pH self-testing devices also may offer benefit in reducing inappropriate self-treatment with antifungal products.

Table 8–1 lists the classic signs and symptoms of the three most common vaginal infections and describes differentiating factors helpful in diagnosis.^{1,3,8,11–16}

Vulvovaginal Candidiasis

VVC is also referred to as a *yeast infection* or *moniliasis*. This condition is one of the most common vaginal infections, with nearly 75% of women reporting at least one VVC infection over their lifetimes.² Recurrent infections occur in less than 5% of women.³ Approximately 20% of women may be colonized with *C. albicans* without experiencing vaginal symptoms.^{2,17,18}

Pathophysiology of Vulvovaginal Candidiasis

Candida fungi are the causative organisms of VVC, with approximately 80%–92% of cases caused by *C. albicans*.³ The incidence of non-*C. albicans* infections has increased in the past 2 decades. *Candida glabrata*, *Candida tropicalis*, and *Saccharomyces cerevisiae* now account for approximately 10% of fungal vaginal infections.^{3,6} This increase may be a result of the widespread use of nonprescription antifungals, short courses of topical imidazole therapy, and long-term suppressive therapy with imidazole antifungals.³

No single causative factor has been identified for most episodes of VVC. Pregnancy, high-dose combined oral contraceptives, and estrogen therapy may affect vaginal pH and the vaginal susceptibility to *Candida* vaginal infections. During the reproductive years, the vaginal epithelium cells are thick and continually provide the lactobacilli, of the primary flora, with glycogen to produce lactic acid.^{19,20} Women with diabetes are at increased risk for *Candida* vaginal infections, particularly if their glycemic control is poor. Antibiotics also may increase the risk of these infections. Between 25% and 70% of women in studies reported acquiring *Candida* vaginal infections during or just after treatment with antibiotics such as tetracycline, ampicillin/amoxicillin, and cephalosporins.²¹ The proposed mechanism is a decrease in normal vaginal flora, especially lactobacilli, allowing an overgrowth of *Candida* organisms. However, neither an increase in vaginal *Candida* organisms nor a decrease in lactobacilli occurs in all women who take these antibiotics. In addition, patients who have received an organ transplant, have HIV infection, or are taking systemic corticosteroid, antineoplastic, or immunosuppressant drugs also may be at increased risk for developing *Candida* vaginal infections.

An increased frequency of VVC may be associated with the onset of regular sexual activity. However, neither the number of sexual partners nor the frequency of sexual intercourse is related to occurrence of VVC episodes.³ Evidence has suggested an increased risk of VVC associated with receptive oral sex.¹ In addition, use of an intrauterine or vaginal sponge contraceptive increases the risk for VVC.³

A consistent association between tight-fitting, nonabsorbent clothing or pantyhose and the development of VVC has not been demonstrated. Clothing of this type, however, may increase risk by creating a warm and moist

environment. Dietary factors such as regular consumption of yogurt may be beneficial in decreasing the symptoms of VVC, but further research is needed.²²

Treatment for *Candida* vaginal infections does not typically include treatment of the male partner, nor has such treatment been shown to prevent recurrence of *Candida* vaginal infections in women. In women who have recurrent infections or when male partners have balanitis, the men may be treated with a topical imidazole.¹¹ If treatment is necessary, topical imidazoles may be applied to the affected area twice a day for 2–4 weeks.

Clinical Presentation of Vulvovaginal Candidiasis

The characteristic signs and symptoms of VVC are listed in [Table 8–1](#). *Candida* vaginal infections typically do not alter vaginal pH, so a pH greater than 4.5 may indicate a bacterial or trichomonal vaginal infection.¹⁹ Use of vaginal pH self-testing devices can assist patients in distinguishing *Candida* vaginal infections that can be self-treated from infections that require medical evaluation and prescription drug therapy. The user-friendly kits use a color test to determine vaginal pH. Limitations with some products include the fact that testing cannot occur until 72 hours after the use of any vaginal preparation, such as a contraceptive spermicide or an antifungal product, and 48 hours after sexual intercourse or douching. In addition, the product cannot be used until 5 days after a menstrual period.

Algorithm: Vulvovaginal Candidiasis

Figure 8–1 Self-care for vulvovaginal candidiasis. Key: BV = bacterial vaginosis; CAM = Complementary and alternative medicine; HIV = human immunodeficiency virus; VVC = vulvovaginal candidiasis. (Source: [References 1, 3, 11, 13, and 14.](#))

Treatment of Vulvovaginal Candidiasis

The treatment of VVC is determined by the severity of symptoms and the frequency of episodes. VVC can be categorized as uncomplicated or complicated, with recurrent VVC considered a complicated infection.² Recurrent or complicated infections are reported in approximately 5% of women; they may be related to host factors such as an inability of normal flora to prevent *Candida* colonization or the presence of potentially resistant organisms.²³

Treatment Goals

The goals of therapy for vaginal fungal infections are relief of symptoms, eradication of the infection, and reestablishment of normal vaginal flora. A single course of drug therapy is effective in achieving these goals for most women. Some women will experience persistent or recurrent infections and will require prolonged therapy or higher dosages of medication.

General Treatment Approach

Self-treatment for VVC with nonprescription antifungal therapy is appropriate for women with uncomplicated disease, infrequent episodes, and mild to moderate symptoms. Women with more severe symptoms, predisposing illnesses or medications, or recurrent infections should be referred to their primary care provider for assessment and treatment.

Recurrent VVC is defined by the occurrence of least four documented infections in a 1-year period.³ Patients should be evaluated for the possibility of a mixed infection or a strain other than *C. albicans*. In addition, frequent or recurrent episodes of VVC may be an early sign of HIV infection or diabetes. The U.S. Food and Drug Administration (FDA) requires labels of nonprescription drug products to include a warning similar to the following²⁴:

Frequent vaginal infections or recurring infections that do not clear up easily with proper treatment require medical evaluation. Possible causes of the infection include pregnancy or a serious underlying medical disorder, such as diabetes or a weakened immune system including exposure to HIV, the virus that causes acquired immunodeficiency syndrome.

Preventive measures are not a standard part of therapy for *Candida* vaginal

infections. Women with frequent infections or those unresponsive to usual treatments may try dietary changes and other nondrug measures, such as avoidance of nonabsorbent clothing. A 3- to 4-month trial of these approaches is sufficient to determine whether they are useful for individual patients.¹ [Figure 8–1](#) outlines the approach to treating a patient with vaginal symptoms.

Nonpharmacologic Therapy

Consumption of yogurt-containing live cultures may potentially decrease VVC episodes, particularly for women who experience recurrent infections.^{1,22}

Discontinuing a drug known to increase susceptibility to *Candida* vaginal infections may potentially be effective in decreasing their incidence. Low-dose oral contraceptives are unlikely to contribute to the occurrence of VVC, but discontinuation of these agents may be tried to determine whether the frequency of infection is altered. Another form of contraception should be recommended and initiated before discontinuation of the oral contraceptive. Patients taking antibiotics or immunosuppressant drugs should consult their primary care provider about these medications.

Pharmacologic Therapy

Vaginal Antifungals

A nonprescription FDA-approved imidazole regimen is the recommended initial therapy for uncomplicated VVC and relief of external vulvar itching and irritation associated with the infection. Approved nonprescription drugs include clotrimazole, miconazole, and tioconazole, which are available as vaginal creams, suppositories, and tablets. [Tables 8–2](#) and [8–3](#) provide proper dosing and administration guidelines, respectively.

Table 8–2 Selected Nonprescription Vaginal Antifungal Products and Their Dosages		
Trade Name	Primary Ingredient	Dosage
Clotrimazole Products		
Gyne-Lotrimin 7	Clotrimazole	Insert cream into vagina daily for 7 days; apply to vulva twice

Trade Name	Primary Ingredient	Dosage
Cream	1%	daily as needed for itching.
Mycelex-7 Cream		
Mycelex-7 Combination Pack	<i>Tablet:</i> clotrimazole 100 mg <i>Cream:</i> clotrimazole 1% ^b	Insert tablet into vagina daily for 7 days; apply cream to vulva twice daily as needed to relieve itching for up to 7 days.
Gyne-Lotrimin 3 Cream	Clotrimazole 2%	Insert cream into vagina daily for 3 days; apply to vulva twice daily for itching.
Miconazole Nitrate Products		
Monistat 1 Combination Pack Day or Night	<i>Cream:</i> miconazole nitrate 2% ^b <i>Suppository:</i> miconazole nitrate 1200 mg	Apply cream to vulva twice daily as needed to relieve itching for up to 7 days; insert suppository into vagina daily (morning or at bedtime) for 1 day.
Monistat 3 Combination Pack ^a Vagistat 3 Combination Pack ^a	<i>Cream:</i> miconazole nitrate 2% ^b <i>Suppository:</i> miconazole nitrate 200 mg	Apply cream to vulva twice daily as needed for itching up to 7 days; insert suppository into vagina daily for 3 days.
Monistat 3 Cream ^a	Miconazole nitrate 4%	Insert cream into vagina daily for 3 days; apply to vulva twice daily as needed for itching.
Monistat 7 Suppository	Miconazole nitrate 100 mg	Insert suppository into vagina daily for 7 days at bedtime.
Monistat 7 Cream	Miconazole nitrate 2%	Insert cream into vagina daily for 7 days; apply to vulva twice daily as needed for itching.
Monistat 7 Combination Pack	<i>Cream:</i> miconazole nitrate 2% ^b <i>Suppository:</i>	Apply cream to vulva twice daily as needed for itching up to 7 days; insert suppository into vagina daily for 7 days.

Trade Name	Primary Ingredient	Dosage
	miconazole nitrate 100 mg	
Tioconazole Products		
Vagistat-1 Ointment 1-Day	Tioconazole 6.5%	Insert ointment into vagina daily for 1 day.
Monistat-1 Day		

^a Prefilled applicators are available for this product.

^b Use for more than 7 days is not recommended. If no symptom relief occurs, patients should see their primary care provider.

Table 8–3 Guidelines for Applying Vaginal Antifungal Products

1. Start treatment at any time of day or prior to going to bed. Lying down will reduce leakage of the product from the vagina.
2. Wash the entire vaginal area with mild soap and water, and dry completely before applying the product.
3. *Vaginal cream:* (If prefilled applicators are being used, skip to step 4.) Unscrew the cap; place the cap upside down on the end of the tube. Push down firmly until the seal is broken. Attach the applicator to the tube by turning the applicator clockwise. Squeeze the tube from the bottom to force the cream into the applicator. Squeeze until the inside piece of the applicator is pushed out as far as possible and the applicator is completely filled with cream. Remove the applicator from the tube. *Vaginal tablets or suppositories:* Remove the wrapper and place the product into the end of the applicator barrel.
4. While standing with feet slightly apart and knees bent, as shown in drawing A, or while lying on your back with knees bent, as shown in drawing B, gently insert the applicator into the vagina as far as it will go comfortably.
5. Push in the inside piece of the applicator, and place the cream as far back in the vagina as possible. To deposit vaginal tablets or suppositories, insert the applicator into the vagina and press the plunger until it stops.
6. Remove the applicator from the vagina.

7. After use, recap the tube (if using cream). Then clean the reusable applicator by pulling the two pieces apart and washing them with soap and warm water. Throw away disposable applicators after 1 use. 8. If desired, wear a sanitary pad to absorb leakage of the vaginal antifungal. Do not use a tampon to absorb leakage, as this will absorb the medication and reduce its efficacy. 9. Continue using the product for the length of time specified in the product instructions. Use the product every day without skipping any days, even during menstrual flow.	

The major effect of antifungals is alteration of fungal cell membrane permeability. These drugs inhibit cytochrome P450 (CYP) enzymes in the cell membrane, thereby decreasing synthesis of the fungal sterol ergosterol. The reduced membrane content of ergosterol is accompanied by an increase in lanosterol-like methylated sterols. These sterols cause structural damage to fungal membranes, resulting in the loss of normal membrane function.

Systemic absorption of clotrimazole is approximately 3%–10%, with negligible absorption for miconazole and tioconazole.^{25–28} Adverse effects from topical imidazoles include vulvovaginal burning, itching, and irritation in 3%–7% of patients.^{25–27} These adverse effects are more likely to occur with the initial application of the vaginal preparation and are similar to symptoms of the vaginal infection. This vaginal irritation may be dose-related, so selecting a product formulation with a longer course and lower strength may help. Abdominal cramps (3%), penile irritation, and allergic reactions (3%–7%) are uncommon, and headache may occur in up to 9% of women.¹

Drug interactions are unlikely because absorption of the antifungals is limited. However, a documented interaction between miconazole vaginal suppositories and warfarin indicates that their concomitant use might pose an increased bleeding risk, because both medications are metabolized by CYP2C9.²⁸ Therefore, pharmacists should contact the patient's primary care provider about possible dosage reductions of warfarin during concurrent therapy, to avoid an increase in the international normalized ratio (INR). The product information advises women using warfarin in combination with these products that bleeding or bruising may occur. Aside from an allergy to imidazoles, contraindications do not exist with the use of topical imidazoles.

Pharmacotherapeutic Comparison

Studies have shown the imidazoles to be equally efficacious, with effectiveness rates of about 80%–90%.^{3,11} A comparison of miconazole single-dose and 7-day treatments has shown similar overall cure rates, with significantly faster rates of symptom relief by day 3 in the single-dose group than in the 7-day treatment group.²⁹ Nonprescription antifungals are available as 7-day regimens of clotrimazole and miconazole; 3-day regimens of clotrimazole and miconazole; and single-dose regimens of clotrimazole, miconazole, and tioconazole. Reviews assessing VVC treatments continue to show similar efficacy among the nonprescription imidazole products.^{14,30}

Several other nonprescription vaginal preparations, such as Vagisil cream, containing benzocaine and resorcinol, also are available. These agents may provide relief of pruritus (itching), but the underlying cause is not addressed. Health care providers should counsel patients on the possible risk of methemoglobinemia associated with benzocaine-containing products.³¹ The use of these agents is therefore rarely, if ever, appropriate, especially in view of the benefits of the imidazole antifungals, including superior efficacy, improved patient adherence, less frequent local reactions, reduced rate of associated adverse effects, and shorter treatment durations. Rarely, products containing benzocaine and resorcinol and medicated douches may be reserved for vaginal and vulvar irritation and itching; they should be used for a limited time only and on the advice of a primary care provider ([Table 8–4](#)).

Table 8–4 Selected Nonprescription Drug Products for Vaginal Itching and Irritation

Trade Name	Primary Ingredient(s)
Pramoxine Products^a	
Vagisil Anti-Itch Original Formula	Benzocaine 5%; resorcinol 2%
Vagisil Maximum Strength	Benzocaine 20%; resorcinol 3%
Hydrocortisone Products^b	
Cortizone-10 Feminine Relief	Hydrocortisone 1%
Povidone/Iodine Products	
Summer's Eve Medicated	Povidone/iodine 0.3% (in disposable bottles)

Trade Name	Primary Ingredient(s)
Douche	
Homeopathic Products	
Yeast-Gard Suppository ^c	<i>Pulsatilla</i> (27×); <i>Candida albicans</i> (27×) <i>Candida parapsilosis</i> (27×)
Yeast-Gard Gel Treatment ^d	<i>Pulsatilla</i> (27×); <i>Candida albicans</i> (27×) <i>Candida parapsilosis</i> (27×)
Other Products	
Summer's Eve Feminine Powder ^e	
Vagisil Feminine Powder ^e	Cornstarch; aloe; mineral oil (in Summer's Eve)

^a Apply benzocaine products externally.

^b Apply hydrocortisone products externally; avoid prolonged use; may use concomitantly with antifungal products.

^c Use 1 Yeast-Gard suppository daily for 7 days.

^d Use 1 Yeast-Gard gel treatment daily as needed.

^e Apply feminine powders externally to absorb moisture.

Product Selection Guidelines

Special Populations

Self-treatment for VVC is not appropriate for patients younger than 12 years of age. This condition is rare in premenarchal girls. Vaginal symptoms in this age group warrant a medical referral to determine the cause. Infections in prepubertal children may indicate potential sexual abuse.³²

Self-care in pregnancy is not appropriate. However, when treatment of VVC is indicated, treatment may consist of the 7-day options of clotrimazole, miconazole, or tioconazole.¹¹ When possible, treatment should be withheld during the first trimester.³² The patient's primary care provider should evaluate for complications, such as hyperglycemia, and assess for other organisms,

because BV and trichomoniasis have the potential for adverse pregnancy outcomes. No special considerations are necessary to treat breastfeeding, older, or immunocompetent women presenting with a VVC infection.¹¹

Patient Factors and Preferences

Selection of cream, tablet, or suppository formulations can be left to the patient, because some women may prefer the convenience of prefilled applicators. Women who have previously experienced VVC may prefer shorter courses of therapy such as single-dose or 3-day options, whereas those who have not had a prior infection opt for more prolonged therapy.¹ Once VVC is confirmed, the decision regarding which product to select should be based on patient preference or other patient-specific factors.³³ If vulvar symptoms are significant, a cream preparation or the combination of a cream with vaginal suppositories or tablets is preferred. Morning or bedtime dosing is available to provide flexibility for patients.

Complementary Therapies

Alternative approaches to treating VVC may include the use of *Lactobacillus* preparations and products such as tea tree oil or boric acid. With *Lactobacillus* products, the rationale for their use is to reestablish normal vaginal flora and inhibit overgrowth of *Candida* organisms. Available data on the effectiveness of this approach, although limited, show benefit for prevention. One study showed a reduction in VVC recurrence with a regimen of *Lactobacillus fermentum* and *Lactobacillus acidophilus* vaginal tablets on alternating days for 10 days followed by 1 vaginal tablet per week for 10 weeks.³⁴ Daily consumption of yogurt with live cultures also may be of some benefit in decreasing VVC symptoms.²² Nonprescription probiotic feminine supplements may be used to reestablish *Lactobacillus*. RepHresh Pro-B probiotic feminine supplement is an easy-to-use product (at a cost of approximately \$25–\$30 for a 30-day supply). Patients take 1 capsule by mouth daily. (See [Chapter 20](#), Table 20–2, for information about probiotics.)

A sodium bicarbonate sitz bath may afford prompt, temporary relief of vulvar irritation associated with a *Candida* vaginal infection before antifungal agents can provide noticeable benefit.³⁵ With resistant VVC infections, tea tree oil may be beneficial owing to its dual antibacterial and antifungal properties.³⁶ A 200-mg vaginal suppository containing tea tree oil may be used once daily for

6 consecutive nights. Allergic dermatitis may occur with this treatment, however. (Further information on tea tree oil is presented in [Chapter 51](#).)

Gentian violet is a topical option used for resistant *Candida* vaginal infections.³⁷ A tampon may be soaked in gentian violet and inserted into the vagina for several hours or overnight. Often a single application is adequate, but tampons saturated with gentian violet can be used once or twice a day for up to 5 consecutive days.

To manage non-*C. albicans* infections, which may be resistant to imidazole antifungals, boric acid may be an effective option. A boric acid 600-mg capsule may be inserted vaginally once daily for 14 days.^{3,11} Short-term cure rates with boric acid demonstrate efficacy, with approximate cure rates of 70% when used in women whose infection did not respond to vaginal antifungals.^{9,11,38} Boric acid capsules may be compounded in community pharmacies. Patient counseling should stress that the capsule is not to be ingested. Pregnant women should not use boric acid.

Assessment of Vulvovaginal Candidiasis: A Case-Based Approach

Many episodes of VVC are uncomplicated and can be effectively treated with topical imidazole agents.³ In particular, the best candidates for self-treatment are otherwise healthy women who experience episodes that are sporadic and uncomplicated and those patients who predictably experience VVC after a course of antibiotic therapy.²¹

Determining the appropriateness of self-care and the likelihood of a *Candida* vaginal infection are important initial steps in advising the patient about the management of vaginal symptoms with nonprescription drug therapy.

Health care providers may advise patients when it is appropriate to self-treat for vaginal symptoms that are consistent with VVC, and when medical evaluation, including pelvic examination and laboratory examination of vaginal secretions, is indicated. Self-treatment is most appropriate when the clinical scenario meets the following four criteria¹¹:

1. Vaginal symptoms are infrequent (i.e., no more than 3 vaginal infections

- per year and no vaginal infection within the past 2 months).
2. A medical practitioner diagnosed at least 1 previous episode of VVC.
 3. Symptoms are mild to moderate and consistent with the characteristic signs and symptoms of VVC, particularly in the absence of a foul odor to the discharge.
 4. If measured, vaginal pH is 4.5 or lower.

Case 8–1 provides an example of the assessment of a patient presenting with a vaginal infection.

Patient Counseling for Vulvovaginal Candidiasis

Counseling of patients who are considering self-treatment with vaginal antifungals should emphasize limiting this approach to management of mild to moderate classic symptoms, infrequent vaginal symptoms, and predictable antibiotic-associated VVC. Patients with possible recurrent infections or with predisposing illnesses are not candidates for self-care; they should be advised to see their primary care provider and may require treatment with prescription options. Therefore, a medical evaluation should be obtained if symptoms persist beyond 1 week after treatment or if they recur within 2 months. Also, if vaginal symptoms occur more than 3 times in a 12-month interval, further evaluation is needed. Women taking warfarin should be referred to their primary care provider.

Patients should be informed that a single-dose to 7-day course of a nonprescription vaginal antifungal product will kill the yeast organisms that caused the infection. Label instructions should be reviewed in appropriate detail. Use of the product only once a day for the specified length of time should be stressed. The patient should be advised that symptomatic relief will likely begin within 2 or 3 days but that it may take a week for complete resolution of symptoms. The patient also should be provided with a list of signs and symptoms indicating the need for medical evaluation. The box “Patient Education for Vulvovaginal Candidiasis” lists specific information for patient counseling.

Case 8–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient reports experiencing vaginal pruritus (itching) with discharge for the past 4 days.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Patient does not report any relevant factors.
c. Description of the patient's efforts to relieve the symptoms	Patient reports that she has not tried anything yet.
d. Patient's identity	Bonnie Stickly
e. Patient's age, gender, height, and weight	34 years, female, 5 ft 5 in., 130 lb
f. Patient's occupation	Chef
g. Patient's dietary habits	Reports eating 3 regular meals/day, with 1 or 2 snacks in between.
h. Patient's sleep habits	Reports sleeping about 7–8 hours each night.
i. Concurrent medical conditions, prescription and nonprescription	Seasonique 1 tablet daily; loratadine 10 mg as needed for seasonal allergies.

Relevant Evaluation Criteria	Scenario/Model Outcome
medications, and dietary supplements	
j. Allergies/other adverse reactions to medications	Sulfa (rash)
k. History of other adverse reactions to medications	None
l. Other (describe)	Per her medical history, Mrs. Stickly has been diagnosed with previous VVC infections, with her most recent infection 4 years ago. She indicates her current discharge is white and she does not notice an odor. She states the symptoms remind her of previous VVC infections.
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s) (Table 8–1).	Mrs. Stickly has itching and white discharge without an odor, findings consistent with a <i>Candida</i> vaginal infection.
3. Identify exclusions for self-treatment (Figure 8–1).	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer Mrs. Stickly for medical evaluation. (2) Recommend self-treatment with an OTC vaginal antifungal product to Mrs. Stickly. (3) Take no action.
Plan	
5. Select an optimal	Mrs. Stickly has symptoms associated with an uncomplicated VVC

Relevant Evaluation Criteria	Scenario/Model Outcome
therapeutic alternative to address the patient's problem, taking into account patient preferences.	infection. She has had a previous VVC infection and reports no chronic medical problems. She is a candidate for self-treatment. (See Figure 8-1 .)
6. Describe the recommended therapeutic approach to the patient or caregiver.	"There are several nonprescription vaginal antifungal products available. Given the bothersome vulvar itching, a combination product with a suppository and a cream may be preferred to assist in relieving your symptoms." (See the box "Patient Education for Vulvovaginal Candidiasis" for instructions on proper use.)
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"This treatment is appropriate because you have symptoms common with vulvovaginal candidiasis infections, your symptoms are mild to moderate, and you have no contraindications or exclusions to self-treatment. It is recommended that you see your primary care provider if your symptoms do not subside within 3 days or are not gone within 1 week; if the vaginal discharge changes (especially if it becomes malodorous or changes presentation from white to yellow); or if your symptoms return within the next 2 months."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
a. Appropriate dose and frequency of administration	"Insert the clotrimazole cream vaginally once daily for 3 days; apply externally to the vulva as needed to relieve itching for up to 7 days."
b. Maximum number of days the therapy should be employed	"Insert the cream for 3 days."
c. Product administration	See Table 8-3 .

Relevant Evaluation Criteria	Scenario/Model Outcome
procedures	
d. Expected time to onset of relief	"Relief should occur within the first 3 days; often initial relief occurs within hours of the first application."
e. Degree of relief that can be reasonably expected	"All symptoms typically resolve within 1 week after beginning treatment."
f. Most common adverse effects	"Vulvovaginal burning and itching are the most common adverse effects."
g. Adverse effects that warrant medical intervention should they occur	"Significant stinging, burning, or itching that persists beyond the first 48 hours of treatment should be medically evaluated."
h. Patient options in the event that condition worsens or persists	"See your primary care provider if symptoms do not lessen in 3 days or they worsen."
i. Product storage requirements	"The product should be stored in a cool area; storage in the bathroom or bedside is appropriate for ease of use."
j. Specific nondrug measures	None
Solicit follow-up questions from patient or caregiver.	(1) "Are any of the nonprescription vaginal antifungal products more effective than another?"
	(2) "Can probiotics also treat this infection?"
Answer patient's or caregiver's questions.	(1) "No, all of the products and regimens are equally effective in treating this infection."
	(2) "Probiotics may be helpful with prevention of infections and may decrease VVC recurrences. The OTC imidazoles are preferred for treatment."
Follow-up: Monitor and Evaluate	

Relevant Evaluation Criteria	Scenario/Model Outcome
9. Assess patient response.	Ask the patient to contact you regarding her treatment outcome. Alternatively, you could call her in a week to evaluate her response to the treatment.
	You called Mrs. Stickly 1 week later, and she reported that her symptoms had resolved.

Key: OTC = Over-the-counter; VVC = vulvovaginal candidiasis.

Evaluation of Patient Outcomes for Vulvovaginal Candidiasis

Symptoms of VVC should lessen within 2 or 3 days of initiation of therapy and resolve within 1 week. The length of treatment, particularly for single-dose and 3-day treatments, does not directly correspond with the time to resolution of symptoms.

The health care provider should advise the patient to call if symptoms persist. With any selected regimen, the importance of adherence must be emphasized. Persistent or new symptoms that are not consistent with VVC constitute a reason for advising the patient to seek a medical referral.

Atrophic Vaginitis

Atrophic vaginitis is inflammation of the vagina related to atrophy of the vaginal mucosa secondary to decreased estrogen levels.

Although up to 45% of postmenopausal women may experience symptomatic atrophic vaginitis, only a small percentage may seek treatment.⁴ *Dyspareunia*, or painful intercourse, is a symptom sometimes related to inadequate vaginal lubrication or atrophic vaginitis.

Pathophysiology of Atrophic Vaginitis

During menopause, the postpartum period, and breastfeeding, the vaginal epithelium becomes thin, and vaginal lubrication declines because of a decrease in estrogen levels. Women may experience atrophic vaginitis and dyspareunia during these intervals.⁴ Atrophic vaginitis also may occur among women with decreased ovarian estrogen production, such as that caused by radiation therapy or chemotherapy. Women taking gonadotropin-releasing hormone (GnRH) agonists, antiestrogenic drugs, and aromatase inhibitors also may experience atrophic vaginitis.⁴

Patient Education for Vulvovaginal Candidiasis

The goals of self-treatment are to cure the vaginal fungal infection and to reestablish normal vaginal flora. Carefully following the product instructions and the self-care measures will help ensure optimal therapeutic outcomes.

Nondrug Measures

- If significant irritation of the vulva is present, take a sodium bicarbonate sitz bath to provide relief and allow the antifungal medication time to become effective.
 - Add 1 teaspoon sodium bicarbonate to 1 pint of water.
 - Add 2–4 tablespoons of the solution to 2 inches of bath water.
 - Sit in the sitz bath or bathtub for 15 minutes as needed for symptom control.
- For recurrent infections, try eating yogurt (1 cup per day of live-culture yogurt) and decreasing dietary sugar and refined carbohydrates.

Nonprescription Medications

- Insert the antifungal product into the vagina once a day, preferably at bedtime to minimize leakage from the vagina. Use a sanitary pad or panty liner to avoid staining of underwear.
- **Table 8–3** provides instructions on administering vaginal antifungals. Significant relief of symptoms should occur within 24–48 hours, and relief is often apparent within hours after the first dose. However, the length of treatment (particularly for single-dose to 3-day treatments) does not directly correspond with the time to resolution of symptoms.
- Continue the therapy for the recommended length of time, even if symptoms have resolved. Stopping treatment early is a common reason for recurrence of vaginal symptoms and, possibly, colonization with difficult-to-treat organisms.
- Vaginal antifungals can be used during a menstrual period. If desired, wait and treat the infection after menses ends. Do not interrupt a course of therapy if menses begins.
- Do not use tampons or douche while using a vaginal antifungal and for 3 days after use.
- Although adverse effects are uncommon, the first dose of the antifungal may cause some vaginal burning and irritation, and a few women (about 1 in 10) experience a headache.
- Refrain from sexual intercourse during treatment with the vaginal antifungal. Vaginal lubricants and vaginal spermicides should not be used at the same time as the vaginal antifungal. Vaginal antifungals can damage latex condoms and diaphragms and may result in unreliable contraceptive effects. Do not use these contraceptives during therapy or for 3 days after therapy, because the antifungal medication remains in the vagina for several days.

When to Seek Medical Attention

- Do not use vaginal antifungals if
 - You have not been medically diagnosed with VVC at least once.
 - You are younger than 12 years of age.
 - You are pregnant.
 - You have diabetes; are positive for human immunodeficiency

virus (HIV) or have acquired immunodeficiency syndrome (AIDS); or have impaired immune function, including that due to certain medications with effects on the immune system.

- You are using warfarin.

When to Seek Medical Attention

- Seek medical attention if symptoms do not lessen within 3 days or symptoms persist beyond 7 days.
- Seek medical attention if vaginal symptoms worsen or change, especially if the vaginal secretions begin to smell bad or become frothy or discolored, or if other symptoms (e.g., abdominal tenderness) occur. These events may indicate that the *Candida* (yeast) organisms are resistant to the nonprescription therapy or that another type of vaginal infection is present.

Clinical Presentation of Atrophic Vaginitis

Atrophic vaginitis is associated with a decrease in vaginal lubrication.⁴ Other manifestations include vaginal irritation, dryness, burning, itching, and dyspareunia. A thin, watery (occasionally bloody), or yellow malodorous vaginal discharge or “spotting” also may be present.^{3,4,6} Sexual activity may result in vaginal bleeding or spotting. A new episode of postmenopausal vaginal bleeding warrants medical referral to rule out endometrial cancer.

Treatment of Atrophic Vaginitis

Self-treatment for atrophic vaginitis is limited to alleviating the primary symptom, vaginal dryness, with lubricant products. To alleviate vaginal dryness in women experiencing moderate to severe symptoms, estrogen therapy may be required. Women who are breastfeeding or have recently given birth often experience a temporary decline in estrogen levels. Vaginal lubricants may be

needed only until estrogen levels return to normal.

Treatment Goals

The goals of therapy are to reduce or eliminate the symptoms of vaginal dryness, burning, and itching, and to eliminate dyspareunia if vaginal dryness is the cause of painful sexual intercourse, by providing lubrication to vaginal tissue.

General Treatment Approach

Vaginal dryness may often be treated with a variety of lubricants such as those listed in [Table 8–5](#). Self-treatment is appropriate when the symptoms are mild to moderate and confined to the vaginal area and when no bleeding is present. Women with severe vaginal dryness, dyspareunia, or bleeding should be referred for medical evaluation.

Table 8–5 Selected Nonprescription Vaginal Lubricants	
Trade Name	Primary Ingredient(s)
Astroglide; K-Y Personal Lubricant Liquid ^a	Glycerin; propylene glycol; hydroxyethylcellulose
K-Y Liquibeads	Glycerin; dimethicone; dimethiconol; gelatin
K-Y Warming Liquid Personal Lubricant	Propylene glycol; hydroxypropylcellulose; tocopherol; PEG 8
Replens Gel Silky Smooth Personal Lubricant	Glycerin; mineral oil

^a Fragrance-free formulation.

Key: PEG = Polyethylene glycol.

[Figure 8–2](#) outlines the approach to treating vaginal dryness associated with atrophic vaginitis.

Nonpharmacologic Therapy

Vaginal Lubricants

Multiple water-soluble products, including Astroglide, K-Y Jelly, and Replens, are available for vaginal lubrication. Personal lubricant products temporarily moisten vaginal tissues. These products provide short-term improvement of symptoms such as burning and itching. Personal lubricants also can provide vaginal lubrication to facilitate sexual intercourse.⁴

Petroleum jelly should not be used because it is difficult to remove from the vagina. Only water-soluble lubricants should be used with a latex condom or diaphragm, because other products may damage the latex and impair the efficacy of these contraceptive devices. Water-soluble lubricant gels can be applied both externally and internally. Initially, the patient should be instructed to use a liberal quantity of lubricant (≤ 2 teaspoons) and then to tailor the quantity and frequency of use to her specific needs. If the patient is self-treating for dyspareunia, the lubricant should be applied to both the vaginal opening and the penis. If the use of lubricants does not produce adequate benefit or is esthetically unappealing to the patient, she should be referred for medical evaluation.

Algorithm: Atrophic Vaginitis

Figure 8–2 Self-care for atrophic vaginitis. (Source: [Reference 4.](#))

Assessment of Atrophic Vaginitis: A Case-Based Approach

When discussing a complaint of vaginal dryness during the patient assessment, the health care provider should obtain a description of signs and symptoms, including any association with sexual intercourse and their severity. This assessment also should ascertain whether the woman has recently given birth, is lactating, or is perimenopausal or postmenopausal. In addition, the use of any vaginal or feminine hygiene products that may cause or worsen vaginal

irritation and dyspareunia should be identified.

Case 8–2 provides an example of the assessment of a patient presenting with atrophic vaginitis.

Patient Counseling for Atrophic Vaginitis

The health care provider should stress the short-term nature of the tissue changes leading to atrophic vaginitis in women who are breastfeeding or who have recently given birth. Women who are perimenopausal or postmenopausal should be advised that long-term treatment with vaginal lubricants may be necessary. In either case, the health care provider should explain the proper use of lubricants for treatment of vaginal dryness or dyspareunia. The box “Patient Education for Atrophic Vaginitis” lists specific information to provide in patient counseling.

Case 8–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient is experiencing vaginal irritation, dryness and dyspareunia. She reports experiencing these symptoms for several weeks.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Symptoms are worse during intercourse.

Relevant Evaluation Criteria	Scenario/Model Outcome
c. Description of the patient's efforts to relieve the symptoms	Patient reports that she has tried OTC lubricants sometimes during intercourse but still has symptoms.
d. Patient's identity	Kerry Korr
e. Patient's age, gender, height, and weight	50 years, female, 5 ft 4 in., 139 lb
f. Patient's occupation	Jewelry store owner
g. Patient's dietary habits	Reports eating 3 meals per day, with 2 snacks/day as needed.
h. Patient's sleep habits	Reports sleeping 7–8 hours per night.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Daily multivitamin
j. Allergies/other adverse reactions to medications	NKDA
k. History of other adverse reactions to medications	None
l. Other (describe) -----	Ms. Korr is postmenopausal and experiencing vaginal irritation, dryness, and dyspareunia not relieved by OTC lubricants. Per her medical history, she has tried such lubricants sometimes during intercourse and has no prior use of estrogen therapy. She reports a history of a hysterectomy 1 year ago.
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Ms. Korr is postmenopausal. She has vaginal irritation, dryness and dyspareunia but no symptoms indicative of other vaginal infections. These symptoms are consistent with atrophic vaginitis.
3. Identify exclusions for self-treatment (Figure 8-2).	She has vaginal irritation, dryness, and dyspareunia as her primary symptoms. She has tried OTC lubricants during

Relevant Evaluation Criteria	Scenario/Model Outcome
	intercourse with minimal relief.
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required and share this information with the patient or caregiver.	Options include (1) Educate Ms. Korr on using the OTC lubricants more frequently. She may use the lubricants daily, as well as during intercourse. (2) Refer Ms. Korr to her primary care provider for possible vaginal estrogen therapy. (3) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Because Ms. Korr has dyspareunia as one of her symptoms and has tried OTC lubricants during intercourse with minimal relief, she is not a candidate for self-care. The recommended option for this patient is to see her primary care provider to further assess her dyspareunia and vaginal irritation and dryness. Her primary care provider may explore the use of vaginal estrogen therapy to relieve the patient's symptoms.
6. Describe the recommended therapeutic approach to the patient or caregiver.	See the box "Patient Education for Atrophic Vaginitis."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"With your vaginal dryness and dyspareunia symptoms, I recommend that you follow up with your primary care provider to consider the use of a vaginal estrogen product. They are generally more effective than lubricants and moisturizers for atrophic vaginitis, such as the product you have been trying. However, you may still use your nonprescription lubricant to assist you with some symptom relief until you see your primary care provider."
Implement	
8. When recommending self-care with nonprescription	Criterion does not apply in this case.

Relevant Evaluation Criteria	Scenario/Model Outcome
medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
Solicit follow-up questions from patient or caregiver.	(1) "I was using my lubricant sometimes with intercourse. How often may I use this nonprescription lubricant?"
	(2) "Will I have to take oral estrogen?"
Answer patient's or caregiver's questions.	(1) "A liberal quantity (2 teaspoons) of nonprescription lubricants may be used as frequently as needed. You may try daily and during intercourse to see if it relieves your symptoms before seeing your primary care provider."
	(2) "Oral estrogen therapy usually is not needed for the treatment of atrophic vaginitis. Typically, the use of vaginal estrogen products (creams, tablets or vaginal rings) will offer relief of symptoms."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact the patient in 1-2 days to follow up and confirm she has made an appointment for further evaluation and medical care.

Key: NKDA = No known drug allergy; OTC = over-the-counter.

Patient Education for Atrophic Vaginitis

The objective of self-treatment with vaginal lubricants is to relieve vaginal dryness and pain during sexual intercourse related to atrophic vaginitis. Carefully following product instructions and the self-care measures listed

here will help to ensure optimal therapeutic outcomes.

- Apply the vaginal lubricant as frequently as needed for relief of vaginal dryness, irritation, burning, or itching, or for inadequate vaginal lubrication.
- Begin treatment for atrophic symptoms with a liberal quantity of lubricant (2 teaspoons); tailor subsequent doses to the quantity and frequency of use needed to provide relief.
- If using lubricants at the time of sexual intercourse, apply the lubricant to the vagina, particularly at the vaginal opening, and to the penis.
- Some leakage of product will occur. If desired, use a sanitary napkin or panty liner to avoid staining of underwear.
- Relief of symptoms may be apparent within hours after the first dose. Regular application of a lubricant can reverse atrophic symptoms to some extent.
- If no improvement is noticeable within a week, or if symptoms worsen or there is any vaginal bleeding, see your primary care provider.

Evaluation of Patient Outcomes for Atrophic Vaginitis

Symptoms of atrophic vaginitis typically lessen within a week of initiation of treatment. The health care provider should advise the patient to call to discuss treatment effectiveness if concerns arise, and to call after 1 week of treatment to report progress in symptom resolution. Persistence of symptoms or the presence of bleeding necessitates medical evaluation.

Vaginal Douching

Prevalence of Douching

The Centers for Disease Control and Prevention reports that 18.8% of U.S. women practice douching.³⁹

A common reason stated for douching is to achieve good vaginal hygiene.^{40,41} Because vaginal douches mechanically irrigate the vagina, clearing away mucus and other accumulated debris, these products may be considered for use as cosmetic cleansing agents. Douching products may vary by ingredients, such as water/vinegar (acetic acid) or povidone/iodine products.

Potential Adverse Effects of Douching

Douching may lead to adverse health outcomes. Douching has been associated with an increased risk for PID, ectopic pregnancy, vaginal infections such as BV, and preterm delivery.^{40,41} Additional problems may include irritation or sensitization from douche ingredients and disruption of the normal vaginal flora and vaginal pH. Allergic reactions may occur with intravaginal povidone/iodine, because systemic absorption is possible. Products containing this combination agent should not be used by women who are allergic to iodine. [Table 8–4](#) lists examples of douche products that contain povidone/iodine.

Use of Douching Equipment

Two types of syringes are available for douching purposes: douche bags and bulb douche syringes. The douche bag, or fountain syringe or folding feminine syringe, holds 1–2 quarts of fluid and comes with tubing and a shutoff valve. Two types of tips are supplied: one for enema use (the shorter rectal nozzle) and a longer one for douching. The two tips are not interchangeable; vaginal infections may occur if a single tip is used for both douching and enemas.

Bulb douche syringes are available as both disposable and nondisposable products. The nondisposable units hold 8–16 ounces of fluid, whereas the disposable units contain 3–9 ounces. The flow rate is regulated by the amount

of hand pressure exerted when the bulb is squeezed. Gentle pressure is recommended, because excess pressure may force fluid through the cervix, causing uterine inflammation. Instructions on proper use of the device are presented in [Table 8–6](#).

Table 8–6 Administration Guidelines for Douches

Bulb Douche Syringe Method

- Choose a comfortable douching position. Two positions are recommended: (1) sitting on the toilet or (2) standing in the shower. Whichever position is chosen, remember that douching is easier when the user is relaxed.
- Gently insert the nozzle about 3 inches into the vagina. Avoid closing the lips of the vagina.
- Squeeze bottle gently, letting solution cleanse the vagina and then flow freely from the body.
- After douching, throw away bottle and nozzle, if they are disposable.

Douche Bag Method

- Fill the douche bag with the prescribed solution or with a warm water and vinegar solution.
- Lie back in the tub with knees bent. Place the douche bag about 1 foot above the height of hips. Do not place or hang the bag any higher because such height will cause the pressure of fluid entering the vagina to be too high.
- Insert the nozzle several inches into the vagina. Aim the nozzle up and back toward the small of the back. While holding the labia closed around the nozzle, release the clamp slowly to allow fluid to enter the vagina. Rotate the tip and allow fluid to enter the vagina until the vagina feels full. Stop the flow of fluid; then hold the fluid in the vagina for about 30–60 seconds. Release and allow the fluid to flow out; repeat until the douche bag is empty.
- Wash the nozzle with mild soap and water.

Patient Counseling for Douching

In the patient assessment, the health care provider should ascertain the woman's reasons for douching. The possible adverse consequences of douching should be clearly identified, with emphasis that this practice is not necessary for internal cleanliness because the vagina is self-cleansing. Douching for routine hygienic purposes should be discouraged, and douching is contraindicated during pregnancy. Douching should be delayed at least 6–8 hours after sexual intercourse if a vaginal spermicide was used as a contraceptive agent.

An alternative cleansing method for vaginal and perineal areas should be

suggested, such as using the fingers to gently wash the outer vaginal area and the vulvar, perineal, and anal regions with lukewarm water and mild soap. If a woman is douching to prevent or treat symptoms of a vaginal infection, such as an abnormal vaginal discharge, she should be counseled about more effective therapy or referred for medical evaluation, as appropriate.

Patients for whom douches have been prescribed or those who insist on douching for other reasons should be instructed on how to use these products safely and effectively. The box “Patient Education for Douching” lists specific information to provide in patient counseling.

Patient Education for Douching

Women should be informed that douching is not necessary for cleansing of the vagina. An alternative cleansing method for vaginal and perineal areas should be suggested, such as using the fingers to gently wash the outer vaginal area and the vulvar, perineal, and anal regions with lukewarm water and mild soap. Improper methods of douching or too-frequent douching can cause vaginal irritation. Douching also can increase the risk for adverse outcomes such as pelvic inflammatory disease. Strictly following the product instructions and the self-care measures listed here will help avoid these problems.

- Keep all douche equipment clean.
- Use lukewarm water to dilute products.
- Follow the appropriate instructions in [Table 8–6](#) for the method of douching being used.
- Never instill the douche solution with forceful pressure.
- Do not use these products for birth control.
- Do not douche until at least 6–8 hours after intercourse during which a diaphragm, cervical cap, or contraceptive jelly, cream, or foam was used.
- Do not douche for at least 3 days after the last dose of vaginal antifungal medication.
- Do not douche for 48 hours before any gynecologic examination.
- Do not douche during pregnancy unless under the supervision of a

primary care provider.

- Use douches only as directed and as recommended by a primary care provider.
- Do not douche more often than twice a week, except on the advice of a primary care provider.
- If vaginal dryness or irritation occurs, discontinue use of the douche.

Key Points for Vaginal and Vulvovaginal Disorders

- Vaginal symptoms often are nonspecific, and it may be difficult to distinguish among symptoms of the three common vaginal infections. The feature most likely to differentiate a *Candida* vaginal infection from BV and trichomoniasis is absence of an offensive odor of the vaginal secretions. Measurement of vaginal pH (pH >4.5 rules out a *Candida* infection) also may help to identify *Candida* infection and to reduce inappropriate use of nonprescription vaginal antifungals.
- *Candida* vaginal infections typically are caused by *C. albicans*, but non-*C. albicans* vaginal infections have increased in frequency. The latter may be more resistant to nonprescription vaginal antifungals.
- Self-treatment for a *Candida* vaginal infection is most appropriate when the patient's symptoms are mild to moderate, when she does not have predisposing illnesses or is taking predisposing medications, when she has had one previously diagnosed infection, and when her symptoms are not recurrent. Recurrent infections are defined as more than three infections occurring within a 12-month period and symptoms recurring within 2 months of previous vaginal symptoms.

- The nonprescription vaginal antifungals are equally effective. Selection of length of regimen or time of day for administration may be determined by patient preference. A medical referral is advised for women taking warfarin. Patients should be informed that symptoms typically lessen within 2 or 3 days after initiation of the nonprescription vaginal antifungals and resolve within a week. The length of the treatment regimen does not directly correspond with resolution of symptoms.
- Use of a sodium bicarbonate sitz bath may provide relief of pruritus (itching) and irritation before the onset of definitive benefit from the antifungal.
- Daily consumption of yogurt with live cultures may benefit some patients in preventing recurrent VVC infections.
- Atrophic vaginitis may occur after menopause, after giving birth, during breastfeeding, or as a result of antiestrogenic medications. Vaginal dryness and dyspareunia may be relieved with use of topical personal lubricant products. If symptoms persist, medical evaluation is needed.
- Atrophic vaginitis may cause vaginal bleeding. Any patient who reports postmenopausal bleeding should be referred to an appropriate health care provider to rule out endometrial cancer.
- Douching is not recommended for vaginal cleansing, because douching can have adverse consequences. Douching is contraindicated during pregnancy. Douching should be postponed until at least 6–8 hours after sexual intercourse if a vaginal spermicide was used for contraception.

Chapter 9: Disorders Related to Menstruation

Authors: Nardine Nakhla

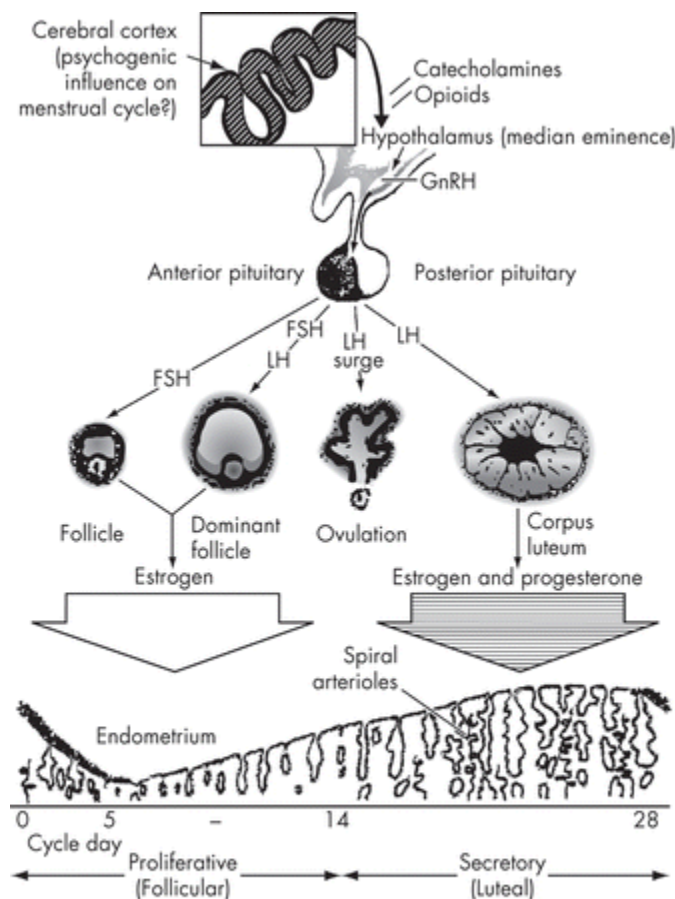
The menstrual cycle is a regular physiologic event for women that begins in adolescence and usually continues through late middle age. Women are able to self-treat for two common menstrual disorders: primary dysmenorrhea and premenstrual syndrome (PMS). Many women use nonprescription products and seek advice from health care providers on how best to manage symptoms of these disorders, including abdominal pain and cramping, irritability, and fluid retention.¹ An understanding of the menstrual cycle will help both patients and health care providers make informed and appropriate decisions about selfcare. Familiarity with common menstrual symptoms and disorders, as well as the risks for toxic shock syndrome, also will support optimal self-care management.

Menstruation results from the monthly cycling of female reproductive hormones. A *single menstrual cycle* is the time between the onset of one period of menstrual flow (menstruation or menses) and the onset of the next. The average age at *menarche* (the initial menstrual cycle) in U.S. women is 12 years, although normal menarche may occur as early as age 11 or as late as age 14.5.¹ The onset of menstruation is influenced by factors such as race, genetics, nutritional status, and body mass. Menarcheal age has important health implications, as early menarche has been linked to breast and endometrial cancer and late menarche is associated with osteoporosis and increased fracture risk.²

The median menstrual cycle length is 28 days, with a range of 25–34 days for adult women; adolescents show more variability, with long cycle lengths and bleeding irregularities in the first 5 years after menarche until regular ovulatory cycles are established with hormonal maturation.³ The menstrual period lasts 3–7 days, with most blood loss occurring during days 1 and 2.^{1,3} The major components of menstrual fluid are blood and endometrial cellular debris; the average blood loss per cycle is 30 mL, with a range of 10–84 mL.³ A loss of more than 80 mL per cycle or bleeding lasting longer than 7 days is considered abnormal and has classically been defined as *menorrhagia*. Excessive and/or prolonged uterine bleeding requires thorough investigation, as it has been

associated with severe anemia and significant impairments in daily functioning.

The menstrual cycle ([Figure 9-1](#)) results from the combined hormonal activity of the hypothalamus, pituitary gland, and ovaries; this is known as the hypothalamic-pituitary-ovarian (HPO) axis. The hypothalamus plays the key role in regulating the menstrual cycle by producing gonadotropin-releasing hormone (GnRH). Low levels of both estradiol and progesterone, present at the end of the previous menstrual cycle, stimulate the hypothalamus to release GnRH, which stimulates pituitary gonadotroph cells to synthesize and secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH).



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Figure 9-1 Hormonal and anatomic relationships during menstrual cycle. The ovarian hormones estradiol and progesterone provide feedback to the pituitary and the hypothalamus. Key: FSH = Follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone.

(Source: Reprinted with permission from Mattox JH. Normal and abnormal uterine bleeding. In: Mattox JH, ed. *Core Textbook of Obstetrics and Gynecology*. St. Louis, MO: Mosby-Yearbook; 1998:397.)

Two principal reproductive events occur during each menstrual cycle: the maturation and release of an ovum (egg) from the ovaries and the preparation of the endometrial lining of the uterus for the implantation of a fertilized ovum. The events of the menstrual cycle can be described in phases that reflect changes in either the ovary (follicular/ovulatory and luteal phases) or the uterine endometrium (menstrual/proliferative and secretory phases). The follicular/ovulatory phase coincides with the menstrual/proliferative phase, and the luteal phase coincides with the secretory phase.

Cycle day 1 is the first day of menstrual flow and the beginning of the follicular and menstrual/proliferative phases. The follicular phase lasts an average of 14 days, ranging in length from several days to several weeks, and ends with ovulation. During the follicular phase, FSH stimulates the maturation of a group of ovarian follicles. These maturing follicles secrete estradiol promoting growth of the uterine endometrium.

By approximately day 8 of the menstrual cycle, a single ovarian follicle usually becomes dominant, and the remaining follicles will undergo atresia. Anti-Müllerian hormone (AMH) plays a role in the selection of this dominant follicle, which typically results in the release or ovulation of only one mature egg. The ovulatory phase of the cycle is about 3 days in length. During this phase, the pituitary gland secretes high levels of LH for a 48-hour period, which is known as the LH surge. The LH surge catalyzes the final steps in the maturation of the ovum and stimulates production of prostaglandins and proteolytic enzymes necessary for ovulation. Estradiol levels decrease during the LH surge, sometimes resulting in midcycle endometrial bleeding. Ovulation typically occurs 12 hours after the LH surge. Ovulation releases 5–10 mL of follicular fluid, which contains the oocyte mass and prostaglandins; this event may be associated with abdominal pain (*mittelschmerz*, German for “middle pain”) for some women.

The *luteal phase* is the time between ovulation and the beginning of menstrual blood flow. After the follicle ruptures, it is referred to as the corpus luteum. The luteal phase is typically consistent in length (about 14 ± 2 days) in

all women and reflects the 10- to 12-day functional period of the corpus luteum. The corpus luteum secretes progesterone, estradiol, and androgens. The increased levels of estrogen and progesterone alter the uterine endometrial lining. Glands mature, proliferate, and become secretory as the uterus prepares for the implantation of a fertilized egg. Progesterone and estrogen levels increase in the middle of the luteal phase, but LH and FSH levels decline in response to the increased hormone levels. If pregnancy occurs, human chorionic gonadotropin released by the developing placenta supports the function of the corpus luteum until the placenta develops enough to begin secreting estrogen and progesterone. If pregnancy does not occur, the corpus luteum ceases to function. Estrogen and progesterone levels then decline, causing the endometrial lining of the uterus to become edematous and necrotic. The decrease in progesterone also leads to prostaglandin synthesis. Following prostaglandin-initiated vasoconstriction and uterine contractions, sloughing of the outer two endometrial layers occurs. The decline in estrogen and progesterone results in an increase in GnRH and in the renewed production of LH and FSH, which begins a new menstrual cycle.

Dysmenorrhea

Dysmenorrhea, defined as painful menstruation, is the most common gynecologic problem among adolescents and young adult women. The prevalence of dysmenorrhea is highest in adolescence, with up to 93% of girls being affected.^{4,5} Dysmenorrhea is divided into primary and secondary disorders by etiology. *Primary dysmenorrhea* is associated with cramp-like lower abdominal pain at the time of menstruation in the absence of pelvic disease. Primary dysmenorrhea usually develops within 6–12 months after menarche, generally affecting women during their teens and early 20s.⁶ Primary dysmenorrhea occurs only during ovulatory cycles. Its prevalence increases between early and older adolescence as the regularity of ovulation increases and decreases after age 24.^{4,6,7}

Approximately 10% of women with dysmenorrhea have secondary dysmenorrhea.⁸ As opposed to primary dysmenorrhea, which is menstrual pain without underlying disease, *secondary dysmenorrhea* is typically associated with pelvic pathology. *Endometriosis* is the most common cause of secondary dysmenorrhea and involves growth of cells similar to endometrial cells in locations outside the uterus. *Adenomyosis*, which is growth of

endometrial tissue into the *myometrium*—the muscular wall of the uterus—is another common cause of secondary dysmenorrhea.⁹ An *ectopic pregnancy*, a potentially life-threatening condition in which a fertilized egg implants outside of the uterus, may manifest with signs and symptoms mimicking severe dysmenorrhea and requires emergent referral. Because of the risk of serious complications, ectopic pregnancy should be considered in all women of childbearing age with vaginal bleeding and/or abdominal pain, especially if the history includes amenorrhea for longer than 4 weeks and/or pregnancy status is unknown.

Secondary dysmenorrhea should also be suspected if symptoms first appear 2 years or more after menarche, if pelvic pain occurs at times other than during menses, or if the patient has irregular menstrual cycles or a history of pelvic inflammatory disease (PID), dyspareunia, or infertility.^{4,5,10} In these situations, referral to a primary care provider is required to identify the underlying cause of dysmenorrhea, so that treatment can be targeted appropriately.

Dysmenorrhea is the leading cause of school absenteeism and lost working hours among adolescent girls and young women. About 26% of adolescent girls report dysmenorrhea-related school absenteeism, which increases to 50% among those who report severe pain.¹⁰ In addition, adolescents with severe menstrual pain reported that the pain interferes with function in other aspects of daily life, such as social activities, sports, work, and relationships with friends and family.^{4,10} Similarly, an estimated 600 million work hours are lost annually because of dysmenorrhea.⁷

The decreased prevalence and severity of dysmenorrhea in women in their mid-20s and older may be partially attributed to a higher rate of pregnancy in this age group, as well as more frequent use of OCs, an effective therapy for primary dysmenorrhea. With use of OC regimens, the thickness of the endometrium decreases, resulting in lower prostaglandin production. Prostaglandins are thought to induce ischemia and hypoxia, resulting in dysrhythmic uterine contractions and decreased blood flow (see “Pathophysiology of Primary Dysmenorrhea” for more detail), so reduced prostaglandin synthesis with use of OCs may decrease the symptoms of dysmenorrhea.¹¹ During the last trimester of pregnancy, uterine adrenergic nerves virtually disappear, and only a portion of the nerves regenerate after childbirth. For many women, this phenomenon results in a decreased prevalence of primary dysmenorrhea following childbirth.¹²

Factors other than young age (under 30) and nulliparity can increase the risk for or severity of primary dysmenorrhea.⁸ These include early menarche (before age 12); heavy menstrual flow; tobacco smoking; a body mass index of less than 20 kg/m²; premenstrual symptoms; history of sexual assault; and stress, anxiety, and depression.^{5,13} Low intake of fruits and vegetables, fish, milk, and other dairy products also may increase the risk of dysmenorrhea: A recent systematic review suggested that increased consumption of these foods may be associated with reduced menstrual pain.¹⁴ Obesity is linked to early menarche and can predispose the patient to primary dysmenorrhea.⁷ In addition, factors such as stress and attempting to lose weight can make dysmenorrhea pain more troublesome.¹²

Pathophysiology of Primary Dysmenorrhea

The cause of primary dysmenorrhea is not fully understood. However, prostaglandins and leukotrienes contribute substantially to the occurrence and severity of dysmenorrhea.^{4,5,7} Abnormal levels of nitric oxide and vasopressin also may be involved.^{5,7} Ovulation increases serum progesterone, which leads to increases in arachidonic acid. During menstruation, arachidonic acid is converted to prostaglandins and leukotrienes, which are then released from lysing endometrial cells in an ovulatory cycle. Prostaglandin levels are 2–4 times greater in women with dysmenorrhea than in women without dysmenorrhea; the severity of dysmenorrhea is proportional to the endometrial concentration of the prostaglandin F₂α (PGF₂α).⁶ *Leukotrienes*, inflammatory mediators known to cause vasoconstriction and uterine contractions, are elevated in women with dysmenorrhea. Leukotrienes may contribute significantly to dysmenorrhea in women who do not respond to NSAIDs.⁷ Conversely, nitric oxide, a substance that promotes uterine quiescence during pregnancy and stops uterine contractility when given during premature labor, may reduce dysmenorrhea pain.⁷ In fact, transdermal nitroglycerin patches, which increase nitric oxide levels, have been shown to decrease dysmenorrhea-related pain. Circulating levels of *vasopressin* (a substance that can produce dysrhythmic uterine contractions) are higher in women with dysmenorrhea than in asymptomatic individuals; however, the role of vasopressin in the etiology of primary dysmenorrhea remains controversial.^{4,5}

Prostaglandins stimulate uterine contractions. Normal contractions and

vasoconstriction help expel menstrual fluids and control bleeding as the endometrium sloughs. However, the increased levels of prostaglandins and leukotrienes typical with dysmenorrhea can lead to strong uterine contractions similar to those experienced during labor and excessive vasoconstriction, resulting in uterine ischemia and pain. In women without dysmenorrhea, uterine contractions are rhythmic, and contraction pressure reaches 120 mm Hg. In contrast, women with dysmenorrhea have more frequent contractions, with pressures up to 180 mm Hg that contribute to ischemia and tissue hypoxia and, thus, pain.

Clinical Presentation of Primary Dysmenorrhea

The pain with primary dysmenorrhea is cyclic in nature and is directly related to the onset of menstruation, usually subsiding within 2 or 3 days ([Table 9–1](#)). Pain is typically experienced as a continuous dull ache, with spasmodic cramping in the lower midabdominal or suprapubic region that may radiate to the lower back and upper thighs. The uterine contractions can force prostaglandins and leukotrienes into the systemic circulation, causing additional symptoms such as nausea, vomiting, fatigue, dizziness, bloating, diarrhea, and headache.⁴ In a large study in adolescents, the most common menstrual symptoms reported were fatigue (78%), cramping (71%), and headaches (64%).¹⁰ Other symptoms included lower back pain (58%) and nausea (37%).¹⁰ Clinical presentation can be adequate for the diagnosis of primary dysmenorrhea, if the pain is mild to moderate in intensity and responds to NSAID therapy.⁴

Table 9–1 Differentiation of Primary and Secondary Dysmenorrhea

Characteristics	Primary Dysmenorrhea	Secondary Dysmenorrhea
Timing/age at onset of dysmenorrhea symptoms	As soon as 6–12 months after menarche but typically several years later; age 13–17 years for most girls	At least 2 years after menarche but more typically mid- to late 20s or older, or pain begins after years of normal cycles.
Cause	Idiopathic; no identifiable pelvic	Associated with pelvic pathology

Characteristics	Primary Dysmenorrhea	Secondary Dysmenorrhea
	pathology	
Menses	More likely to be regular with normal blood loss	More likely to be irregular; menorrhagia and intermenstrual bleeding more common
Pattern and duration of dysmenorrhea pain	Onset just before or coincident with onset of menses; pain with each or most menstrual periods, lasting only 2–3 days	Pattern and duration vary with cause; change in pain pattern or intensity also may indicate secondary disease.
Pain at other times of menstrual cycle	No	Yes; may occur before, during, or after menses
Response to NSAIDs and/or OCs	Yes	Depends on the cause of secondary dysmenorrhea. Pain with mild–moderate endometriosis may respond to OCs or other hormonal contraceptives, but response to NSAIDs often is absent or inadequate. Adenomyosis is not responsive to NSAIDs or hormonal contraceptives.
Other symptoms	Fatigue, headache, nausea, change in appetite, backache, dizziness, irritability, and depression may occur at same time as dysmenorrhea pain.	Vary according to cause of the secondary dysmenorrhea; may include dyspareunia, pelvic tenderness

Key: NSAID = Nonsteroidal anti-inflammatory drug; OC = oral contraceptive.

Source: References 4 and 8–10.

Treatment of Primary Dysmenorrhea

Many women use nonprescription products to self-treat dysmenorrhea. In one study examining in adolescents, 66% self-treated with analgesics; of those, 78% used nonsalicylate NSAIDs; fewer used acetaminophen or aspirin.¹⁰ Inadequate management of dysmenorrhea pain can lead to increased pain sensitivity at

times other than during menses and to increased sensitivity to nonuterine pain, thus having important implications for pain perception and quality of life.⁹

Treatment Goals

The goals of treating primary dysmenorrhea are to resolve or provide significant improvement in symptoms (pain) and to minimize the disruption of usual activities.

General Treatment Approach

An important initial step in managing dysmenorrhea is distinguishing between primary and secondary dysmenorrhea by obtaining a thorough patient history. The medical history should include age at menarche, menstrual cycle characteristics (length, regularity, amount of bleeding, correlation with pain symptoms), and length of time elapsed between menarche and the onset of dysmenorrhea.¹³ Associated symptoms (e.g., headache), other health conditions (e.g., sexually transmitted infections), allergies, medications (including previous therapies), and relevant social history such as smoking and sexual activity should be explored.

Self-care is appropriate for otherwise healthy young women who have a history consistent with primary dysmenorrhea and are not sexually active and for those who have been previously diagnosed with primary dysmenorrhea.⁴ Adolescents with pelvic pain who are sexually active are at risk for PID and should be referred for further medical evaluation. Referral also is warranted for women with characteristics suggesting secondary dysmenorrhea ([Table 9–1](#)).

A variety of therapies are indicated for the management of dysmenorrhea. NSAIDs and hormonal contraceptives are both viable first-line options.¹⁵ Treatment choice is influenced by whether or not the affected individual desires hormonal contraception, previous medication experience(s), and other patient preferences. An estimated 80%–90% of women with primary dysmenorrhea can be successfully treated with NSAIDs, hormonal contraceptives, or both. Other treatment options include use of dietary supplements (e.g., omega-3 fatty acids). [Figure 9–2](#) presents an algorithm for managing primary dysmenorrhea.

A patient with more severe dysmenorrhea, a change in the pattern or intensity of pain, or inadequate response or intolerance to NSAIDs should be referred to her primary care provider. An estimated 15% of women do not respond to NSAIDs, cannot tolerate therapy, or prefer not to use medication for dysmenorrhea.⁹Figure 9–2 lists exclusions for self-care.

Nonpharmacologic Therapy

Many women use nonpharmacologic measures adjunctively to help manage dysmenorrhea and menstrual discomfort. These strategies may be especially useful for women who cannot tolerate or do not respond to nonprescription medications. A study of adolescents found that these nonpharmacologic interventions included sleep, hot baths or a heating pad, and exercise.⁴ The use of heat is a commonly recommended nondrug therapy. Heat therapy is thought to relieve menstrual pain through vasodilation, which increases blood flow to the area and relaxes smooth muscle. An abdominal heat wrap has been tested for the treatment of dysmenorrhea and in one study provided 14% greater pain relief than acetaminophen.¹⁶ In another study, a heating patch plus placebo pill was found to be comparable in efficacy to ibuprofen plus unheated patch for pain relief. Combining the heating patch and ibuprofen conferred no additional benefit in terms of pain relief, however, time to onset was shorter.¹⁶ A recent systematic review examining the effectiveness of nondrug modalities in primary dysmenorrhea concluded that heat therapy has a moderate reduction in menstrual pain compared to placebo and only a small to moderate reduction in pain intensity when compared to analgesic medication control groups.¹⁶ Evidence regarding the benefit of exercise is conflicting; however, participation in regular exercise may lessen the symptoms of primary dysmenorrhea for some women.^{4,5} The mechanism by which exercise provides pain relief is not clear; however, many theories have been proposed, including stress reduction, antinociceptive effects, and decreased prostaglandin levels. Findings in studies examining low-intensity exercise have been more favorable, with yoga and stretching showing significant pain reduction when compared with no treatment.¹⁶

Smoking and exposure to secondhand smoke have been associated with more severe and/or chronic dysmenorrhea.^{4,16} The severity of dysmenorrhea symptoms reportedly increases with the number of cigarettes smoked per day. The basis for this effect is unknown, but nicotine-induced vasoconstriction may be involved. Discontinuing tobacco smoking or avoiding exposure to

tobacco smoke may decrease symptoms. Pharmacists can assist patients in smoking cessation efforts.

Pharmacologic Therapy

Unfortunately, in many women and adolescents with dysmenorrhea, their symptoms remain untreated or are inadequately treated. These patients continue to experience pain and limitations in their daily activity. Four nonprescription analgesic medications are commonly used by women in self-treatment for dysmenorrhea: acetaminophen, aspirin, ibuprofen, and naproxen sodium. [Table 9–2](#) lists their dosages for dysmenorrhea. [Chapter 5](#) provides further discussion of their adverse effects, contraindications, and drug interactions. The uses and properties of these four nonprescription agents are summarized next, followed by a brief discussion of dietary supplements.

Table 9–2 Treatment of Dysmenorrhea With Nonprescription Medications	
Agent	Recommended Nonprescription Dosage (maximum daily dosage)
Acetaminophen	650–1000 mg every 4–6 hours (4000 mg)
Aspirin	650–1000 mg every 4–6 hours (4000 mg)
Ibuprofen	200–400 mg every 4–6 hours ^b (1200 mg)
Naproxen sodium	220–440 mg initially; then 220 mg every 8–12 hours (660 mg)

Note: See Table 5–5 for information on clinically important drug interactions with nonprescription analgesic agents

^a If the dosage 200 mg every 4–6 hours is ineffective, the recommended dosage for dysmenorrhea (400 mg every 6 hours while awake) should be taken.

Aspirin

Aspirin may be adequate for treating mild symptoms of dysmenorrhea. In typical analgesic dosages, aspirin has only a limited effect on prostaglandin synthesis and is only moderately effective in treating more than minimal symptoms of dysmenorrhea. In fact, a Cochrane review found that aspirin was no better than placebo in providing pain relief.⁹ Aspirin also may increase

menstrual flow.

Acetaminophen

Acetaminophen may be adequate for treating mild symptoms of dysmenorrhea. Acetaminophen is a weak inhibitor of prostaglandin synthesis; the reduction of $\text{PGF}_2\alpha$ levels is much greater with nonsalicylate NSAIDs than with acetaminophen.^{17,18} Even in dosages of 4 g daily, acetaminophen is less effective than ibuprofen; therefore, lower dosages are less likely to be effective.¹⁷

Nonsalicylate NSAIDs

Nonsalicylate NSAIDs, the first-line agents for treatment for primary dysmenorrhea, include ibuprofen and naproxen sodium ([Table 9–2](#)). In clinical trials, these NSAIDs were effective in 64%–100% of patients.⁹ Relief of dysmenorrhea is typically obtained within the first cycle of use, and symptomatologic improvement is thought to be related to decreased prostaglandin levels with NSAID use. However, dosages used in clinical trials and dosages of prescription drugs for the treatment of dysmenorrhea often are higher than the labeled nonprescription dosages. Therefore, providers may recommend prescription therapy, or they may recommend that a patient who is using nonprescription products try a prescription dosage of an NSAID if the lower dosage does not provide adequate symptom relief.

Therapy with nonsalicylate NSAIDs should begin at the onset of menses or pain. If inadequate pain relief occurs, treatment beginning 1 or 2 days before expected menses may improve symptomatic relief.⁵ This timing often requires that patients track their menstrual cycles to know when to start NSAID use. If the possibility of pregnancy exists, therapy should be initiated only after menses begins (see later under “Special Populations” for more detail). Patients should be instructed that the NSAID is used to prevent cramps and to relieve pain. Optimal pain relief is achieved when these agents are taken on a schedule, rather than on an as-needed basis. Therefore, ibuprofen should be taken every 4–6 hours and naproxen sodium every 8–12 hours for the first 48–72 hours of menstrual flow, because that time frame correlates with maximum prostaglandin release ([Table 9–2](#)). The therapeutic effect usually is apparent 30–60 minutes after administration, and benefit will be optimal with continued regular use.

A patient with dysmenorrhea may respond better to one NSAID than to another. If the maximum nonprescription dosage of one agent does not provide adequate benefit, switching to another agent is recommended. The analgesic effect for most NSAIDs plateaus, so further dosage increases may increase the risk of adverse effects without providing additional benefit. Therapy with NSAIDs should be undertaken for three to six menstrual cycles, with changes made in the agent, dosage, or both before judging the effectiveness of these agents for a particular patient. If nonprescription NSAID therapy does not provide an adequate therapeutic effect, other therapies that may provide relief from primary dysmenorrhea may be tried. These include prescription NSAID therapy; prescription dosages of nonprescription NSAIDs; and/or use of a hormonal contraceptive. Examples of hormonal contraceptives are a combination OC agent, injectable or implantable progestin, an estrogen plus progestin vaginal ring or transdermal patch, and a levonorgestrel intrauterine contraceptive (IUC).¹⁹ In some cases, the combination of a hormonal contraceptive and an NSAID may be required for adequate symptom relief.

The usual adverse effects from a few days of intermittent NSAID use are gastrointestinal (GI) symptoms such as upset stomach, vomiting, heartburn, abdominal pain, diarrhea, and constipation. Adverse effects may also include headache and dizziness. Some GI adverse effects may be decreased by taking the drugs with food.

Dietary Supplements

Although a number of studies have evaluated the use of dietary supplements for dysmenorrhea management, high-quality evidence to support the safety and efficacy of such products is lacking.²⁰ Very limited evidence suggests that fish oil, fenugreek, ginger, valerian, vitamin B₁, vitamin D, zataria, and zinc sulfate may be beneficial.^{15,20,21} In the absence of more robust evidence for most of these supplements, only fish oil and vitamin D are considered here.

Omega-3 fatty acids are found in fish and fish oil and compete with arachidonic acid in the cyclooxygenase and lipoxygenase pathways, leading to a decrease in the production of the proinflammatory cytokines. Increased consumption of fish rich in omega-3 fatty acids from tuna, salmon, and sardines or use of fish oil supplements may reduce symptoms. One study showed that women who received an omega-3 fatty acid supplement (180 mg

eicosapentaenoic acid + 120 mg docosahexaenoic acid) daily for 3 months had improvement in pain intensity and required less ibuprofen than those receiving placebo.²²

Cholecalciferol (vitamin D₃) is known to decrease the production of prostaglandins and to increase prostaglandin inactivation.²³ One small study found a reduction in dysmenorrhea pain among women with low serum vitamin D levels who were given a single 300,000 IU dose of cholecalciferol 5 days before menses.²⁴ More recently, high-dose cholecalciferol (50,000 IU weekly for 9 weeks) was shown to reduce pain severity in adolescent girls.²¹ Because the safety of long-term, high-dose vitamin D₃ is uncertain, women should be counseled to ingest vitamin D₃ 600 IU daily, the recommended daily dietary allowance. These measures often serve as an adjunct to drug therapy.

Pharmacotherapeutic Comparison

A Cochrane review of 80 randomized, controlled trials (RCTs) demonstrated strong evidence to support NSAIDs as first-line agents for primary dysmenorrhea because of their consistent effectiveness in providing moderate to excellent pain relief over that obtained with placebo.¹⁸ There appear to be minimal differences with regard to either efficacy or safety among NSAIDs.¹⁸ Cost, duration of action, tolerability, and availability should guide agent selection. Ibuprofen and naproxen sodium are available without a prescription. Because of restrictions on taking medications to school, adolescents may benefit from naproxen's longer duration of action. Women at risk for GI ulceration should consider the use of a gastroprotective agent or another therapeutic option such as an OC. Acetaminophen may provide some relief for patients with hypersensitivity or intolerance to aspirin and for patients with intolerance to the GI and platelet-inhibition adverse effects of aspirin and other NSAIDs. OCs as well as intravaginal and intrauterine hormonal contraceptives are used for the management of dysmenorrhea. Some trials report benefits with OC therapy in up to 80% of women; however, a Cochrane review found limited evidence of effectiveness in the management of dysmenorrhea.⁸

Product Selection Guidelines

Special Populations

The U.S. Food and Drug Administration (FDA) recommends that aspirin and

aspirin-containing products not be given to children and adolescents who have or are recovering from chickenpox or influenza-like symptoms because of the risk of Reye syndrome.²⁵ (See [Chapter 5](#) for further information.) Pregnant or menopausal women do not experience dysmenorrhea; if cramping/pelvic pain occurs, these patients should be referred to their primary care provider. Women attempting to become pregnant should avoid use of NSAIDs, as these agents may impair implantation of the blastocyst. Acetaminophen and ibuprofen can safely be taken by breastfeeding women because the levels of both medications documented in breast milk are low.²⁶ Women who are breastfeeding should avoid use of high-dose aspirin; low-dose aspirin (75–325 mg daily) is associated with low salicylate levels, and with such regimens the drug does not appear to be excreted into breast milk.²⁶ Naproxen sodium is a less optimal choice for breastfeeding women; although levels in breast milk are low, this medication has a long half-life, and a serious adverse reaction in a neonate has been reported.²⁶ A nonpharmacologic approach such as topical heat application may also be a good choice for breastfeeding women.

Patient Factors

Because NSAIDs are used only temporarily and intermittently, the risk for GI toxicity is limited. However, patients who have active peptic ulcer disease, those at risk for GI bleeding, or those with a history of GI ulcers should discuss use of NSAIDs with their primary care provider. Treatment with acetaminophen, nonpharmacologic therapy, or an OC regimen may be more appropriate. NSAIDs also can inhibit platelet activity and increase bleeding time. Women on anticoagulants should avoid NSAID use, and caution is warranted in women on other agents that may increase bleeding. Women who consume 3 or more alcohol-containing beverages daily should discuss use of acetaminophen or aspirin with their primary care provider, because additive liver or GI toxicity, respectively, may occur.

Patient Preferences

Women may prefer to use an NSAID that they are familiar with, or they may wish to try another agent if adverse effects were experienced previously. Preferences also may be based on tablet/capsule preferences or cost of products.

Complementary Therapies

A Cochrane review found tentative evidence that use of transcutaneous electrical nerve stimulation (TENS) decreases acute pain compared with placebo.²⁷ Another Cochrane review, including 42 RCTs, evaluated the use of acupuncture or acupressure for the treatment of primary dysmenorrhea. Although limited, low-quality studies showed some benefit, the evidence was insufficient to permit overall conclusions regarding safety and efficacy.²⁸ All complementary therapies require further investigation to elucidate their role in the management of dysmenorrhea.

Algorithm: Primary Dysmenorrhea

Figure 9–2 Self-care for primary dysmenorrhea. Key: CAM = Complementary and alternative medicine; GERD = gastroesophageal reflux disease; GI = gastrointestinal; IUC = intrauterine contraceptive; NSAID = nonsteroidal anti-inflammatory drug; OTC = over-the-counter; PID = pelvic inflammatory disease; PCP = primary care provider; PUD = peptic ulcer disease.

Assessment of Primary Dysmenorrhea: A Case-Based Approach

Before recommending any product to a patient experiencing symptoms of dysmenorrhea, the health care provider should ascertain that the symptoms, particularly the onset and duration of pain in relation to the onset of menses, are consistent with primary dysmenorrhea ([Table 9–1](#)).

Case 9–1 illustrates the assessment of a patient with dysmenorrhea.

Patient Counseling for Primary Dysmenorrhea

Adolescents and young women who experience primary dysmenorrhea symptoms should be educated about this condition so they (1) realize primary

dysmenorrhea is normal, (2) recognize typical symptoms and symptoms that are inconsistent with primary dysmenorrhea and when to seek medical evaluation, (3) understand that NSAIDs are preferred therapy because of their efficacy, and (4) know how to use these agents for greatest benefit (e.g., appropriate dose and dosing frequency, when in menstrual cycle to initiate therapy). Patients also should be advised that nonprescription NSAIDs might be appropriate for initial therapy, but that not all women will respond. If response to the first agent is not adequate, another NSAID and/or an OC or a nondrug intervention can be tried. The health care provider should explain the proper use of these agents and their potential adverse effects. Nondrug measures (e.g., topical heat, exercise, dietary changes) also can be tried; however, patients should be advised that these strategies may not be adequate for effective management, so that combination with pharmacologic therapy may be necessary. The box “Patient Education for Primary Dysmenorrhea” lists specific information to provide during patient counseling.

Evaluation of Patient Outcomes for Primary Dysmenorrhea

Patient monitoring is accomplished by having the patient report whether symptoms are improved or resolved. Symptoms should improve within an hour or so of taking an NSAID. The optimal effect of drug therapy may not be seen until the woman has used the medication on a scheduled basis. If inadequate pain relief occurs, treatment beginning 1 or 2 days before expected menses may improve symptomatic relief. The patient with persistent symptoms should be advised to try another nonprescription NSAID, to add adjunct therapy, to consider use of an OC, or to see a primary care provider for evaluation.

Case 9–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms) including age at onset of symptoms	Patient is suffering from abdominal pain, describing it as "menstrual cramps." She regularly experienced menstrual cramping as a young teenager, but it resolved when she started combination OC therapy. The patient discontinued her OC regimen about 5 months ago because she and her husband are trying to conceive. This is the first time she has experienced painful "cramping" with menses since discontinuing the combination OC agent. She reports the pain started suddenly yesterday (day 4 of her menstrual period) and describes it as persistent, sharp, and severe. Her last menstrual period was about 6 weeks ago.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Patient is unable to identify anything that makes the pain better or worse.
c. Description of the patient's efforts to relieve the symptoms	"Yoga used to help when I was a teenager, so I attended a class this morning—but it did nothing."
d. Patient's identity	Jessica Bentley
e. Patient's age, gender, height, and weight	24 years, female, 5 ft 5 in., 130 lb
f. Patient's occupation	Social worker
g. Patient's dietary	Patient describes a well-balanced diet; no food allergies or restrictions.

Relevant Evaluation Criteria	Scenario/Model Outcome
habits	She usually has no issues with appetite, but has been in too much pain to eat anything substantial since yesterday.
h. Patient's sleep habits	She generally sleeps well—about 7 hours each night—but only slept 3 or 4 hours last night.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	<i>Asthma</i> : well-controlled with budesonide 360 mcg BID and albuterol 90–180 mcg every 4–6 hours as needed; <i>prenatal care</i> : 1 prenatal vitamin daily.
j. Allergies	None known
k. History of other adverse reactions to medications	None known
l. Other (describe) -----	n/a
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	The onset and severity of Mrs. Bentley's symptoms are not characteristic of primary dysmenorrhea. Sudden, sharp, and severe abdominal pain presenting on day 4 of menses may indicate underlying pelvic pathology.
3. Identify exclusions for self-treatment (Figure 9-2).	Sudden, sharp, and severe abdominal pain occurring after the onset of menses is inconsistent with primary dysmenorrhea, which generally manifests as dull, crampy pain coinciding with the onset of menses and lasting 2 or 3 days. A referral for further evaluation is necessary in this case to rule out other causes, including ectopic pregnancy, as Mrs. Bentley is actively trying to conceive.
4. Formulate a comprehensive list of therapeutic	Options include (1) Refer Mrs. Bentley to an appropriate health care

Relevant Evaluation Criteria	Scenario/Model Outcome
alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	provider. (2) Recommend self-care with nonprescription and nondrug measures. (3) Recommend self-care until Mrs. Bentley can see an appropriate health care provider. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, considering patient preferences.	Refer Mrs. Bentley for urgent care to rule out ectopic pregnancy.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"The sudden onset and severity of the pain you've described is not typical of primary dysmenorrhea. Because you have been trying to become pregnant, it is important to rule out an ectopic pregnancy and/or any other serious conditions."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Primary dysmenorrhea—which can be self-treated—generally manifests as dull, crampy pain that begins with the onset of menses and lasts 2 or 3 days. With what you've described, there may be something more serious going on, like an ectopic pregnancy. Ectopic pregnancies can be life-threatening if left unidentified, so it is important that you seek medical attention as soon as possible."
Implement	

Relevant Evaluation Criteria	Scenario/Model Outcome
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	n/a
Solicit follow-up questions from the patient or caregiver.	"Could I take ibuprofen to help with the pain while I'm waiting to be seen at the walk-in clinic?"
Answer the patient's or caregiver's questions.	"NSAIDs like ibuprofen and naproxen sodium are not recommended for women trying to become pregnant, as they may make it harder to conceive. Acetaminophen or nondrug strategies like heat therapy may be more appropriate since you and your partner are trying to conceive. With acetaminophen, you can take 650-1000 mg every 4-6 hours, to a maximum of 4000 mg in 24 hours. However, even if this provides some relief, it is still critical that you be seen by a primary care provider to rule out an underlying cause for your pain. Additionally, NSAIDs should be used with caution in asthmatics, as these agents are associated with increased risk of bronchospasm."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	n/a

Key: n/a = Not applicable; NSAID = nonsteroidal anti-inflammatory drug; OC = oral contraceptive.

Patient Education for Primary Dysmenorrhea

The objective of self-treatment is to relieve or significantly lessen symptoms of dysmenorrhea, to limit discomfort and disruption of usual activities. For most patients, carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

Nondrug Measures

- If effective, apply topical heat to the abdomen, lower back, or other painful area.
- Stop smoking cigarettes and avoid secondhand smoke.
- Consider eating more fish high in omega-3 fatty acids or taking a fish oil supplement.
- Participate in regular exercise if it lessens the symptoms.
- No dietary supplements have been shown effective for primary dysmenorrhea.

Nonprescription Medications

- Ibuprofen and naproxen sodium are the best types of nonprescription medication for primary dysmenorrhea. These medications stop or prevent strong uterine contractions (cramping).
- Start taking the medication when the menstrual period begins or when menstrual pain or other symptoms begin. Then take the medication at regular intervals, following the product instructions, rather than just when the symptoms are present. See [Table 9–2](#) for recommended nonsteroidal anti-inflammatory drug (NSAID) dosages.
- Take the NSAID with food to limit upset stomach and heartburn.
- Do not take NSAIDs if you are allergic to aspirin or any other NSAID, or if you have peptic ulcer disease, gastroesophageal reflux disease, colitis, or any bleeding disorder.
- If you have hypertension, asthma, or heart failure, watch for early symptoms that the NSAID is causing fluid retention.
- Do not take a nonsalicylate NSAID if you also are taking anticoagulants or lithium.

When to Seek Medical Attention

- Seek medical attention if the pain intensity increases or if new symptoms occur.
- Seek medical attention if abdominal pain occurs at times other than just before or during the first few days of menses.

Premenstrual Disorders

Almost all women experience some mild physical or mood changes before the onset of menses, and these are normal signs of ovulatory cycles.²⁹ The changes may include physical symptoms; food cravings; and emotional lability, irritability, or lowered mood. In addition, some women report positive changes, including increased energy, creativity, work productivity, and sexual desire.³⁰

Premenstrual disorders are cyclic and composed of a combination of physical, mood, and behavioral symptoms that occur during the luteal phase of the menstrual cycle. Symptoms improve significantly or disappear by the end of menses and are absent during the first week following menses. The number and severity of symptoms and the extent to which they interfere with functioning distinguish typical premenstrual symptoms, PMS, and premenstrual dysphoric disorder (PMDD) from each other ([Table 9–3](#)).³¹ PMS is distinguished from normal physiologic premenstrual symptoms by its negative effect on daily functioning and the extent of distress caused by symptoms. PMDD is a severe form of PMS, and its diagnosis requires documentation of a specific constellation of symptoms that occurs on a cyclical basis, the presence of key psychological symptoms, and severity of symptoms sufficient to interfere with social and/or occupational functioning.²⁹

Of women with PMS, 60%–80% experience only mild, primarily physical symptoms that do not interfere with their lives.³² An estimated 20%–30% of women experience clinically significant symptoms of PMS, and 3%–8% report symptoms that cause significant impairment that interferes with relationships, lifestyle, or work.²⁹

Premenstrual disorders can occur any time after menarche. Symptoms usually begin in the teenage years up to the early 20s; typically, affected patients wait about a decade to seek care.^{4,32} Symptoms occur only during ovulatory cycles and disappear during events that interrupt ovulation, such as pregnancy and breastfeeding, and at menopause. The use of OCs can cause or exacerbate premenstrual disorders, and hormone therapy in postmenopausal women may result in recurrence of symptoms.³³

Many factors contribute to the development of a premenstrual disorder, including genetic predisposition. Twin studies have shown that premenstrual disorders are inherited, with women whose mothers had a premenstrual disorder being more likely to develop such a disorder.^{33,34} In addition, genetic differences exist in the serotonergic 5-hydroxytryptamine (5-HT_{1A}) receptor and the estrogen alpha-receptor gene in women with and without premenstrual disorder symptoms.³⁴ Stress and previous traumatic events, including sexual abuse, also are risk factors for premenstrual disorders. Different coping strategies for handling stress, as well as altered psychological and physiologic responses to stress, have been shown in persons with a history of life stress and abuse.³⁴ Sociocultural factors also can influence the experience of premenstrual symptoms. Exposure to negative expectations about premenstrual symptoms can lead patients to interpret normal symptoms more negatively.³⁴

Pathophysiology of Premenstrual Disorders

The etiology of premenstrual disorders is not fully understood. The current consensus is that the fluctuations of estrogen and progesterone caused by normal ovarian function are the cyclic trigger for premenstrual disorder symptoms. Although these symptoms are triggered by hormonal fluctuations, no known hormonal imbalances are present in women with a premenstrual disorder. Some women are biologically vulnerable or predisposed to experience this type of disorder because of a neurotransmitter sensitivity to physiologic changes in hormone levels.^{4,32,34} Serotonin, which is involved in mood and behavior regulation, is affected by estrogen and progesterone levels. Reduced serotonin in the brain may be linked to symptoms such as poor impulse control, irritability, carbohydrate craving, and dysphoria.^{4,33} Other neurotransmitters and systems that may be important are allopregnanolone and gamma-aminobutyric acid (GABA) receptors. Allopregnanolone is a

progesterone metabolite that binds the GABA receptor, leading to an anxiolytic action.³² Women who have a premenstrual disorder may be less sensitive to the sedating effects of allopregnanolone during the luteal phase and may have different GABA receptor sensitivity.^{32,34} These alterations may result in luteal phase symptoms such as anxiety and irritability.³³ In addition, selective serotonin reuptake inhibitors (SSRIs), which are known to relieve premenstrual disorders, affect the synthesis of allopregnanolone. Therefore, for symptoms severe enough to warrant prescription drug therapy, treatment is based on medications that affect the levels of serotonin or suppress ovulation and interrupt hormonal cycling. Finally, deficiency of certain vitamins and minerals, including pyridoxine (vitamin B₆), calcium, vitamin D, and magnesium, also has been implicated in premenstrual disorders, but studies are limited. The suggested role of these vitamins and minerals in the pathogenesis of premenstrual disorders and supplementation as a means of management are discussed in more detail under “Pharmacologic Therapy.”

Table 9–3 Differentiation of PMS and PMDD From Other Conditions With Luteal Phase Symptoms

Typical premenstrual symptoms	Mild physical (breast tenderness, bloating, low backache, food cravings) or mood (irritability, emotional lability, lowered mood, increased energy or creativity) changes before the onset of menses that do not interfere with normal life functions
Premenstrual syndrome	At least one mood (depression, irritability, anger, anxiety) or physical (breast tenderness, abdominal bloating) symptom during the 5 days before menses. Symptoms are virtually absent during cycle days 5–10. The symptom or symptoms are severe enough to cause significant distress and/or have a negative effect on normal daily functioning (e.g., interfere with work and school performance) or interpersonal relationships. Symptoms may range from mild-moderate to severe.
Premenstrual dysphoric disorder	Five or more symptoms (mood or physical) are present the last week of the luteal phase of the menstrual cycle, with at least one symptom being significant depression, anxiety, affective lability, or anger. The intensity of the symptoms interferes with work, school, social activities, and social relationships. Symptoms should be absent the week after menses and must not be an exacerbation of the symptoms of another disorder such as depression, panic disorder, or personality disorder.
Premenstrual exacerbation of other disorders	A worsening of the symptoms of other, typically psychiatric disorders, such as depression and anxiety or panic disorders. Conditions such as asthma, endometriosis, hypothyroidism, irritable bowel syndrome, attention-deficit/hyperactivity disorder, diabetes, rheumatoid arthritis, migraine headaches, seizure disorders, and perimenopause also can worsen premenstrually. However, symptoms do not occur only during the luteal phase of the menstrual cycle; there is

no symptom-free interval.

Source: References 4, 37, and Petersen N, London ED, Liang L, et al. Emotion regulation in women with premenstrual dysphoric disorder. *Arch Womens Ment Health*. 2016;19(5):891–898. doi: 10.1007/s00737-016-0634-4.

The pathophysiology of physical symptoms of premenstrual disorders (e.g., breast tenderness, bloating, joint/muscle pain) is not as well studied. Studies of fluid retention and breast enlargement have not found tissue changes; abdominal bloating often occurs without weight gain.³¹

Exogenous hormones may influence premenstrual symptoms. Women taking either OCs or postmenopausal replacement hormones may experience adverse effects similar to PMS symptoms as a result of altered hormone levels.^{30,33} Conversely, 71% of women reported that the use of their OC had no effect on their PMS symptoms.⁴ Certain OCs have been useful in reducing the symptoms of premenstrual disorders, particularly those containing drospirenone, formulations with a lower estrogen dose, and products with a shortened hormone-free interval between pill packs or featuring continuous or extended cycles.^{19,29}

Algorithm: Premenstrual Syndrome

Figure 9–3 Self-care for premenstrual syndrome. Key: AIDS = Acquired immunodeficiency syndrome; CAM = complementary and alternative medicine; HT = hormone therapy; MAOI = monoamine oxidase inhibitor; OC = oral contraceptive; OTC = over-the-counter; PMDD = premenstrual dysphoric disorder; PMS = premenstrual syndrome; PUD = peptic ulcer disease; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

Clinical Presentation of Premenstrual

Disorders

The symptoms of premenstrual disorders are not unique to these conditions; however, the occurrence of specific symptoms and their fluctuation with the phases of the menstrual cycle are diagnostic. Premenstrual symptoms typically begin or intensify about a week before the onset of menses, peak near the onset of menses, and resolve within several days after the beginning of menses.³³ Symptoms typically are consistent from month to month. A woman with a premenstrual disorder should experience essentially a symptom-free interval during days 5–10 of her menstrual cycle.

Common symptoms of premenstrual disorders are listed in [Table 9–4](#). Women seeking symptom relief typically report multiple emotional, physical, and behavioral symptoms. Mood symptoms tend to cause more distress than physical symptoms because of their impact on work and personal relationships. A large crosssectional study conducted in multiple countries found that the most common PMS symptoms reported by women included abdominal bloating, cramps or abdominal pain, irritability, breast tenderness, and joint or back pain.³⁵ These symptoms may blur the distinction between dysmenorrhea and PMS, making the timing of symptom onset important for differentiation. Furthermore, the presence of dysmenorrhea may be associated with a greater severity of PMS.³⁶ Mild to moderate PMS generally responds well to self-treatment with nondrug and/or nonprescription therapies (see “Treatment of PMS” for details).

Table 9–4 Common Premenstrual Syndrome Symptoms
Most Common Negative Symptoms
Fatigue, lack of energy
Irritability, anger
Labile mood with alternating sadness and anger
Depression, decreased interest in usual activities
Anxiety, feeling stressed
Crying spells, oversensitivity

Difficulty concentrating
Abdominal bloating, edema of extremities
Breast tenderness
Appetite changes (overeating and food cravings)
Headache
Hypersomnia/insomnia
Joint/muscle pain
Feeling out of control/overwhelmed
Most Common Positive Symptoms
Increased energy, more efficient at work
Increased libido, more affectionate
Increased sense of control, more self-assured

Source: Adapted from [reference 29](#).

Symptoms of PMDD are similar to those of PMS. Compared with women who have PMS, women with PMDD experience more symptoms, symptoms of greater severity, and symptoms that impair personal relationships and the ability to function well at work or school to a greater degree. Among women with PMDD, the most common symptoms are affective in nature. The diagnosis of PMDD requires that a patient experience marked anger or irritability or depressed mood, anxiety, or emotional lability.³⁷ Other signs and symptoms of PMDD include difficulty concentrating, lethargy, hypersomnia or insomnia, and physical symptoms such as breast tenderness and bloating. The severity of symptoms must cause significant impairment in the ability to function socially or at work during the week before menses.³⁷ A daily rating of symptoms for several cycles establishes a diagnosis of PMS or PMDD, and these types of symptoms should have occurred during most menstrual cycles over the past year. PMDD symptoms during the last 7 days of the cycle should

be at least 30% worse than those experienced during the midfollicular phase (days 3–9 of the menstrual cycle). Criteria for a formal diagnosis of PMDD are outlined in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5).³⁷ Patients with suspected PMDD require referral to a primary care provider to ensure proper diagnosis and management.

Premenstrual disorders should be distinguished from typical premenstrual symptoms and also from premenstrual exacerbations of other disorders, particularly mood disorders. Some medical conditions can be aggravated during the premenstrual phase (e.g., hypothyroidism, fibromyalgia).^{33,37} In addition, mood disorders not occurring solely during the luteal phase must be distinguished from cyclic mood symptoms ([Table 9–3](#)). The lack of a symptom-free interval may suggest that the patient has a psychiatric disorder, such as an anxiety or panic disorder, or another health condition such as the menopausal transition, rather than PMS.

Treatment of Premenstrual Syndrome (PMS)

PMS is a cyclic, multisymptom disorder that involves emotional, behavioral, and physical symptoms. A single therapeutic agent is unlikely to address all symptoms. Thus, treatment should be selected to address the patient's most bothersome symptoms. A symptom log or calendar is a useful tool for documenting such symptom(s) and the cyclic nature of this disorder. This information will also be useful in evaluating the efficacy of treatment. In women with severe symptoms, alleviation of symptoms is less likely with use of nonprescription therapies alone. In addition, PMS symptoms are chronic and, in most cases, will continue until menopause. Therefore, the cost of therapy, the possibility that a woman may become pregnant, and the likelihood of adverse effects are important considerations in selecting therapy.

Treatment Goals

The two intended outcomes for women with premenstrual disorders are (1) to better understand premenstrual disorders and (2) to improve or resolve symptoms to reduce the impact on activities and interpersonal relationships. Therapy typically is considered effective if symptoms are reduced by 50% or more.

General Treatment Approach

Mild to moderate PMS symptoms often are self-treatable and do not require prescription drug therapy. In these cases, initial treatment is generally conservative and consists of education and nonpharmacologic measures. Such measures include dietary and lifestyle modifications (e.g., physical exercise, stress management) as well as light therapy, cognitive behavioral therapy, and acupuncture.³³ Women should be educated about the syndrome and encouraged to identify techniques for coping with PMS symptoms and stress. Knowledge about this disorder can allow patients to exert some control over their symptoms. By tracking their menstrual cycle, patients can predict when symptoms will occur and plan accordingly. For example, scheduling more challenging tasks during the first half of the cycle may help limit the influence of this condition on social and work functioning.

Supplements with evidence of potential benefit include calcium, pyridoxine, and chasteberry (*Vitex agnus-castus*).^{33,34} Preliminary data suggest a potential benefit from ginkgo, magnesium pyrrolidone, St. John's wort, and saffron.³⁸

Prescription drug therapy should be considered if the treatments outlined in [Figure 9–3](#) are ineffective or if the patient suffers from moderate to severe PMS or PMDD. SSRIs used daily, only during the luteal phase of the menstrual cycle, or when symptoms occur are the first-line agents for prescription therapy.³⁹ Agents that suppress ovulation such as OCs and GnRH agonists also are used. Newer OC products containing drospirenone or formulated with shortened hormone-free intervals or extended cycling also may be considered first-line therapeutic agents for patients who prefer a gynecologic approach rather than a psychological approach.³⁹ Finally, hysterectomy with bilateral oophorectomy is effective for refractory severe symptoms.⁴⁰ Surgery may be appealing for women experiencing significant adverse drug reactions and/or costs.⁴⁰

Nonpharmacologic Therapy

Several nonpharmacologic therapies may decrease PMS symptoms, including aerobic exercise, dietary modifications, and cognitive behavioral therapy.³³ Exercise can increase endorphin levels and may help decrease PMS symptoms.³³ Although evidence supporting dietary changes is limited, many health care providers recommend eating a balanced diet while also avoiding salty foods and simple sugars, which may cause fluid retention, and avoiding

caffeine and alcohol, which can increase irritability.^{33,34} Cravings for foods high in carbohydrates, which contain the serotonin precursor tryptophan, are common in women with PMS. Two studies of a carbohydrate-rich beverage that increased tryptophan levels demonstrated a reduction of emotional symptoms in women with PMS.³⁴ Consuming foods rich in complex carbohydrates such as whole-grain foods during the premenstrual interval also may reduce symptoms.³⁴

Stress is reported to increase PMS symptoms. Cognitive behavioral therapy, which emphasizes relaxation techniques and coping skills, may be of benefit for stress reduction.^{33,34} These approaches may be helpful used singly or as adjuncts to other therapies. Data that suggest a possible benefit with light therapy, acupuncture, and massage are also available.³³

Pharmacologic Therapy

A survey of women with PMS found that 80% use some nonprescription therapeutic modality including vitamins, minerals, and herbs; a number of products claim benefits for the management of PMS, although little supporting evidence is available.³⁸

Pyridoxine

Pyridoxine (vitamin B₆) has been suggested to provide therapeutic benefit in PMS. Trials have reported mixed results, with no dose–response relationship shown, and no trials were performed in women with PMDD.^{34,38} One double-blind, placebo-controlled trial found that pyridoxine 80 mg daily improved subjective mood to a greater extent than placebo.³⁴ The dosage of pyridoxine should be limited to 100 mg daily because of the risk for peripheral neuropathy with higher dosages.³³

Calcium and Vitamin D

Data show an inverse relationship between both milk and vitamin D intake and PMS.⁴ An additional study reported that high dietary intake of both calcium and vitamin D may prevent the development of PMS symptoms.⁴¹ Calcium ingestion may reduce fluctuations in calcium levels across the menstrual cycle. Hypocalcemia causes affective symptoms (anxiety, irritability, depression) similar to those of premenstrual disorder.²⁹ Reduced levels of

vitamin D secondary to alterations in calcium and vitamin D metabolism during the luteal phase may trigger PMDD symptoms.

Several randomized trials have evaluated the effect of calcium supplementation on PMS symptoms. The largest trial studied the effect of calcium in a dosage of 600 mg twice daily in 466 women with moderate to severe PMS.⁴² Symptoms were significantly reduced by the second month of therapy, and by the third month, calcium had reduced overall symptoms by 48%. Emotional symptoms such as mood swings, depression, and anger, as well as food cravings and physical symptoms, were all reduced. More than one half of the women taking calcium had a greater than 50% reduction in symptoms; almost one third reported a greater than 75% symptomatologic improvement. Few women experienced adverse effects from calcium; five withdrew from the study because of nausea, and one woman each in the calcium and placebo groups developed kidney stones. The dosage of calcium used in the trial is consistent with the recommended daily calcium intake for women of reproductive age, which is between 1000 and 1300 mg daily. Similar improvements were noted in smaller studies.^{31,38,43} Patients should be encouraged to meet daily calcium recommendations through their diet first, but supplementation can be added as needed. Additionally, all health care providers should reinforce adequate calcium and vitamin D intake in women to help prevent osteoporosis.

Magnesium

Magnesium deficiency may lead to some PMS-type symptoms (e.g., irritability), and low magnesium levels in red blood cells have been found in women with PMS. Affective symptoms associated with PMS were reduced by magnesium pyrrolidone carboxylic acid in a dosage of 360 mg daily administered during the luteal phase.^{37,41} By contrast, two trials of magnesium oxide found no benefit. The dosage of magnesium pyrrolidone carboxylic acid used in the trial was similar to the recommended dietary allowance of magnesium for women (310–360 mg). About 50% of women regularly consume less than that amount, and obtaining adequate magnesium from food sources may be difficult. Food sources of magnesium include spinach, Swiss chard, nuts, legumes (e.g., beans, peas), and whole-grain cereals. Adverse effects other than diarrhea are uncommon.

Vitamin E

Although vitamin E deficiency has not been established in women experiencing PMS, limited evidence suggests that supplementation may improve symptoms in some patients. One double-blind, randomized trial, for example, showed that vitamin E at a dose of 100 mg daily for three cycles produced statistically significant reduction in physical and mental symptoms.⁴⁴ Vitamin E supplementation may be considered in the management of PMS; however, because the evidence for use is limited, other options are preferred.

Nonsteroidal Anti-inflammatory Drugs

NSAIDs reduce some of the physical symptoms such as headache and muscle/joint pains and mood symptoms associated with PMS when taken for several days before the onset of and during the first several days of menses.³³ The benefit from these agents may reflect the coexistence of dysmenorrhea and PMS, or PMS manifesting primarily as physical symptoms.

Diuretics

A common premenstrual symptom is the subjective sensation of fluid accumulation, particularly with abdominal bloating. However, most women do not experience any true sodium or water retention and do not experience weight gain.⁴⁵ Two factors may explain the sense of abdominal bloating. First, a distinction must be made between fluid redistribution (in which weight does not change) and fluid retention (which can be detected by weight gain). The abdominal bloating and swelling observed with PMS are primarily caused by a fluid shift to this area. As a result, diuretics that are indicated for relieving fluid retention are unlikely to be helpful for most women with PMS. Second, abdominal distention in this setting may be secondary to relaxation of the gut muscle caused by progesterone.⁴⁵ For women who have true water retention and resultant weight gain, however, a diuretic may be useful.

Over the years, three FDA-approved nonprescription diuretics have been marketed for relieving water retention, weight gain, bloating, swelling, and the feeling of fullness. These agents are ammonium chloride, caffeine, and pamabrom. The last agent is currently the most common diuretic found in nonprescription menstrual products ([Table 9–5](#)).

Table 9–5 Selected Combination Nonprescription Menstrual Products

Trade Name	Diuretic With Dose per Tablet/Capsule	Analgesic and/or Antihistamine With Dose per Tablet/Capsule
Aqua-Ban Tablets; Diurex Max; Diurex Aquagels;	Pamabrom 50 mg	
Diurex Ultra; Diurex Ultimate; Diurex XPL	Caffeine 100 mg	
Diurex Water Pills + Pain Relief	Caffeine 50 mg	Magnesium salicylate 162.5 mg
Pamprin Multi-symptom; Premsyn PMS	Pamabrom 25 mg	Acetaminophen 500 mg; pyrilamine maleate 15 mg
Pamprin Max	Caffeine 65 mg	Acetaminophen 250 mg; aspirin 250 mg
Midol	Pamabrom 25 mg	Acetaminophen 500 mg
Midol Complete	Caffeine 60 mg	Acetaminophen 500 mg; pyrilamine maleate 15 mg
Midol Long Lasting Relief		Acetaminophen (extended-release) 650 mg

Ammonium chloride is an acid-forming salt with a short duration of effect. The drug is taken in oral dosages of up to 3 g daily, divided into 3 doses, for no more than 6 consecutive days. Larger dosages of ammonium chloride can produce significant GI and central nervous system adverse effects. Ammonium chloride is contraindicated in patients with renal or liver impairment, because metabolic acidosis may result. Ammonium chloride is no longer available as a nonprescription drug but can be obtained as a dietary supplement.

Caffeine promotes diuresis by inhibiting the renal tubular reabsorption of sodium and water. In doses of 100–200 mg every 3–4 hours, caffeine is safe and effective, although patients may develop tolerance to its diuretic effect. Caffeine may cause anxiety, restlessness, or insomnia, and it may worsen PMS by causing irritability. Additive adverse effects might occur if other caffeine-containing medications, foods, or beverages, especially “energy drinks,” are consumed concurrently. Caffeine may also cause GI irritation; thus, it can

precipitate or worsen dyspepsia. Patients taking monoamine oxidase inhibitors (MAOIs) or theophylline should also avoid diuretics that contain caffeine.

Pamabrom, a derivative of theophylline, is found in combination products along with analgesics and antihistamines marketed for the treatment of PMS. Pamabrom also is available as a standalone agent in products such as Diurex Max. Pamabrom may be taken in dosages of up to 50 mg 4 times daily.

Combination Products

Multi-ingredient nonprescription products are marketed for women with PMS-type symptoms. Two of the most commonly used product brand names are Midol and Pamprin. Some products contain acetaminophen, caffeine/pamabrom, and pyrilamine, whereas others contain only an NSAID or a combination of an analgesic with a diuretic or an antihistamine ([Table 9–5](#)). Pain is a less common symptom of PMS, and no evidence exists that the sedative effect of an antihistamine, such as pyrilamine, will provide benefit to women experiencing the emotional symptoms of PMS. Therefore, these types of nonprescription products should not be recommended. More appropriate recommendations include the use of specific agents, such as those previously discussed, or referral for prescription drug therapy.

Pharmacotherapeutic Comparison

Calcium can be suggested for the initial treatment of PMS symptoms. If relief is inadequate, another agent from among those just discussed or a combination of two or more agents may be tried. Caffeine or pamabrom can be considered for women experiencing bloating with documented weight gain but may be inappropriate for those with irritability as a PMS symptom. Caffeine and pamabrom should also be used cautiously in patients with a history of peptic ulcer disease and those taking MAOIs or other xanthine medications such as theophylline. NSAIDs should be reserved for women who experience headache, joint and/or muscle pain, or concomitant dysmenorrhea. Use of combination products containing antihistamines should be discouraged, because the resulting drowsiness may impair job performance, schoolwork, and driving.

Product Selection Guidelines

Special Populations

PMS does not occur during pregnancy or after menopause. Adolescents and adult women should initially attempt to manage symptoms with lifestyle changes and therapies such as calcium supplementation. Adolescents should avoid combination products containing aspirin (see “Special Populations” under “Dysmenorrhea”). Women who are breastfeeding should avoid all herbal products, because information about their safety for nursing infants is limited. Vitamins and minerals in the dosages used for PMS are generally compatible with breastfeeding, and magnesium use is unlikely to cause diarrhea in breastfed infants.²⁵ Diuretics should be avoided during breastfeeding, as caffeine appears in breast milk about 1 hour after maternal ingestion. Caffeine may cause fussiness and poor sleep in infants, especially if consumed in high dosages or if the infant is preterm or younger than 3 weeks of age.²⁶

Patient Factors

Patients using proton pump inhibitors and histamine-₂ receptor antagonists should use calcium citrate rather than calcium carbonate products, because the latter products are less soluble with a higher gastric pH.

Patient Preferences

Patient preferences for PMS treatment can be accommodated. Women preferring to use dietary supplements should discuss their use with an HCP to ensure that drug–drug or drug–disease interactions do not exist.

Complementary Therapies

Trials have been conducted with botanical therapies, including chasteberry (*Vitex agnus-castus*), St. John’s wort (*Hypericum perforatum*), ginkgo (*Ginkgo biloba*), and saffron (*Crocus sativus*).³⁶ The first three dietary supplements are discussed in depth in [Chapter 51](#).

Chasteberry has shown efficacy in decreasing mild to moderate PMS symptoms; in four high-quality trials, chasteberry demonstrated a significant improvement over placebo.⁴⁶ Trials have used different formulations of chasteberry. Two trials using a standardized fruit extract, ZE 440, of chasteberry found a significant reduction in PMS symptoms including lower

mood, irritability/anger, pain/headache, breast tenderness, and fluid retention.⁴⁷ Two randomized, double-blind, placebo-controlled trials found that chasteberry extract reduced common PMS symptoms and did not cause any serious adverse effects.^{47,48} Symptoms, including negative affect, water retention, food cravings, and pain, were significantly less troublesome by the end of the third cycle of use.^{47,48} Chasteberry generally is well tolerated, with nausea and headache cited as the most common adverse effects.⁴⁹ Chasteberry may offer more benefit for patients with mild to moderate PMS and for women experiencing breast symptoms.^{49,50} Although evidence for chasteberry in the management of PMS appears favorable, a recent meta-analysis found that the treatment effect may be overestimated owing to study bias, heterogeneity, and potential publication bias. High-quality trials comparing chasteberry with established treatment options are needed to determine its relative efficacy.⁵¹

Chasteberry may affect estrogen receptors and inhibit prolactin.⁵⁰ Women who are pregnant or lactating should avoid chasteberry, and caution is warranted with its use in women taking hormones or who have hormone-sensitive cancers. See [Chapter 51](#) for additional interaction information.

One randomized trial of St. John's wort reported a reduction in anxiety-related symptoms in women with PMS, although its effect was not different from that of placebo.³⁸ St. John's wort may provide symptomatic improvement in persons with mild to moderate depression. Two high-quality trials did not find a benefit greater than that of placebo.⁴⁶ St. John's wort has many clinically significant drug interactions, including reduction in effectiveness of OCs.

A placebo-controlled randomized trial evaluated ginkgo in a dosage of 160–320 mg daily in 165 women with PMS. Breast pain, anxiety, irritability, and depression associated with PMS were improved with ginkgo.^{38,46} Ginkgo has antiplatelet effects and may increase the risk of bleeding.

In one randomized trial comparing saffron extract 30 mg daily with placebo, the saffron extract was found to significantly reduce PMS symptoms and depression symptoms.^{38,46}

Assessment of Premenstrual Syndrome: A Case-Based Approach

The health care provider should obtain a complete description of the patient's symptoms and their timing to determine whether the patient has PMS, PMDD, or another disorder with PMS-type symptoms. The severity of premenstrual disorder symptoms should also be considered in self-treatment. The HCP should identify medications that could be causing the symptoms reported or that may interact with nonprescription agents used to treat PMS (e.g., H₂ receptor antagonists and calcium salts). Previous treatments for the symptoms should also be explored.

Case 9–2 illustrates the assessment of a patient with PMS.

Case 9–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient reports the regular occurrence of PMS symptoms, including irritability, muscle pain, breast tenderness, and food cravings. She describes these symptoms as mild to moderate, affecting her productivity at work and ability to enjoy social events. The symptoms occur in a predictable pattern, starting about a week before menses and resolving within 1 or 2 days of menses onset. She has experienced these symptoms since her teenage years and reports that her mother did as well, before menopause. Currently, she says her irritability and food cravings are her most bothersome symptoms.
b. Description of any factors that seem to	"My symptoms seem to be worse when I'm busy at work and/or home and feeling overwhelmed. Snacking on things like chips and cookies helps with my food cravings, but then I feel guilty for eating junk food. I haven't

Relevant Evaluation Criteria	Scenario/Model Outcome
precipitate, exacerbate, and/or relieve the patient's symptom(s)	noticed anything that helps with my other symptoms."
c. Description of the patient's efforts to relieve the symptoms	"I've never tried anything to help with my symptoms—PMS is just something I've learned to expect and suffer through, but I'm hoping to change that."
d. Patient's identity	Lucy King
e. Patient's age, gender, height, and weight	30 years, female, 5 ft 2 in., 125 lb
f. Patient's occupation	Accountant
g. Patient's dietary habits	Ms. King reports that her diet is "good" overall: She eats a variety of foods (meats, fruits, vegetables, etc.) but is lactose-intolerant so she does not consume dairy products. She admits to snacking on junk food, particularly during the week before menses.
h. Patient's sleep habits	Ms. King has trouble falling asleep when she is feeling overwhelmed with her job or personal life but has no problems staying asleep once sleeping. On average, she sleeps 6–6.5 hours per night.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Ms. King is lactose-intolerant. She takes ranitidine 75 mg twice a day as needed for acid reflux. She does not currently take any dietary supplements.
j. Allergies	Allergic to penicillin

Relevant Evaluation Criteria	Scenario/Model Outcome
k. History of other adverse reactions to medications	The patient has experienced development of hives with penicillin use.
l. Other (describe) -----	n/a
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	The symptoms described (irritability, muscle pain, breast tenderness, food cravings), their negative effect on the patient's productivity and social functioning, and the timing of their onset (a week before menses) and resolution (within 1 or 2 days of menses) are consistent with mild to moderate PMS. The clinical picture is more severe than just typical premenstrual symptoms but does not meet criteria for PMDD or premenstrual exacerbation of other disorders.
3. Identify exclusions for self-treatment (Figure 9-3).	Ms. King has no exclusions for self-treatment: Symptoms occur only during the luteal phase of the menstrual cycle (i.e., there is a symptom-free interval); she is not experiencing significant depression, anxiety, or anger; and her symptoms do not appear to reflect an exacerbation of another disorder.
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the	Options include (1) Refer Ms. King to an appropriate health care provider. (2) Recommend self-care with nonprescription and nondrug measures. (3) Recommend self-care until Ms. King can see an appropriate health care provider. (4) Take no action.

Relevant Evaluation Criteria	Scenario/Model Outcome
patient or caregiver.	
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Dietary and lifestyle modifications should be recommended as initial treatment. This approach includes consuming more foods that are rich in complex carbohydrates and avoiding simple sugars, increasing calcium intake, and implementing stress reduction strategies (e.g., CBT, massage, acupuncture). Keeping a symptom log or calendar also should be recommended to track the symptom pattern and the effectiveness of any interventions. Finally, education on PMS should be provided.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"What you are describing is consistent with mild to moderate PMS. This condition can generally be managed using nondrug and nonprescription therapies. Dietary and lifestyle modifications are often recommended first. To reduce your food cravings, try to eat foods that are rich in complex carbohydrates, like whole-grain foods. Because you are lactose-intolerant, it is also important to ensure you are getting enough calcium. Low calcium levels may contribute to irritability, and ensuring adequate intake can help with this, as well as some of your other PMS symptoms (e.g., physical symptoms and food cravings). Target a calcium intake of 1000–1300 mg daily. Nondairy sources of calcium include beans, almonds, and fortified beverages. Adequate vitamin D (at least 600 IU daily) is also recommended to improve calcium absorption and reduce the risk of osteoporosis. You mentioned that your symptoms are worse when you are overwhelmed at home and/or work, so implementing strategies to reduce stress, like having a massage, is also recommended. Finally, you should track your symptoms using a log or calendar, as this will allow us to identify patterns and evaluate the efficacy of interventions tried."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from	"You indicated that irritability and food cravings were currently your most bothersome symptoms, and these initial recommendations target those symptoms. Dietary and lifestyle modifications have been shown to be safe and effective in the management of PMS, so these strategies have been recommended first. Pharmacologic and complementary therapies can be considered if you do not notice improvement within a few months. Strategies for managing your less-bothersome symptoms (e.g., muscle pain) can be discussed during follow-up or sooner if needed."

Relevant Evaluation Criteria	Scenario/Model Outcome
the considered therapeutic alternatives.	
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	“Consume foods that are rich in complex carbohydrates during the premenstrual interval to reduce food cravings. Foods rich in complex carbohydrates include beans, whole grains, and starchy vegetables (e.g., sweet potatoes). Also ensure you are consuming adequate dietary calcium. Target an intake of 1000–1300 mg daily. Nondairy sources of calcium include beans, almonds, and fortified beverages. Vitamin D (at least 600 IU daily) is also recommended to improve calcium absorption and reduce the risk of osteoporosis.”
Solicit follow-up questions from the patient or caregiver.	“If I can’t get enough calcium from my diet, can I take a calcium supplement?”
Answer the patient’s or caregiver’s questions.	“Yes, but because you use ranitidine for acid reflux, calcium citrate would be preferred over calcium carbonate, as it is better absorbed in these situations. Do not take more than 500–600 mg of elemental calcium at a time.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	“Try these dietary and lifestyle modifications for several months to assess their effectiveness. If you are unable to meet the daily target for calcium intake from your diet alone, we can discuss supplementation with calcium citrate. If your other PMS symptoms (e.g., breast tenderness, muscle pain) become more bothersome and you would like to discuss management strategies before our follow-up, please let me know. Also contact me if you have questions or concerns about any of the strategies we have discussed

Relevant Evaluation Criteria	Scenario/Model Outcome
	today.”

Key: CBT = Cognitive behavioral therapy; n/a = not applicable; OC = oral contraceptive; PMS = premenstrual syndrome; PMDD = premenstrual dysphoric disorder.

Patient Counseling for Premenstrual Syndrome

Patients should receive education on the timing of PMS symptoms and be encouraged to track their symptoms using a symptom log and calendar. This approach will help predict symptom onset and may increase compliance with recommended therapies. Health care providers should be prepared to discuss management strategies for both the behavioral and physical symptoms of mild to moderate PMS. If the patient prefers to use nonprescription medications or vitamins, the proper use and potential adverse effects of these agents should be explained. However, patients should be informed of the limited evidence for efficacy of these agents in treating PMS, so that expectations can be managed accordingly. The patient also should be advised that treatment measures must be implemented during every menstrual cycle, because it may take several cycles for symptomatic relief to occur. The “Patient Education for Premenstrual Syndrome” box lists specific information to provide patients during counseling.

Evaluation of Patient Outcomes for Premenstrual Syndrome

Monitoring is accomplished by having the patient report whether the PMS

symptoms have decreased or resolved. It may take several menstrual cycles to ascertain whether lifestyle changes or nonprescription therapies are reducing the symptoms of PMS. Comparing the occurrence and/or severity of symptoms before and after vitamin or medication use can help determine the value of a therapy. Women should be encouraged to contact the health care provider to discuss treatment effectiveness and to clarify information or answer any questions. Reasons for advising the patient to see her primary care provider include persistent symptoms, symptoms that the patient reports are disruptive to personal relationships, or symptoms that affect the patient's ability to engage in usual activities or function productively at work/school.

Patient Education for Premenstrual Syndrome

The objective of self-treatment for premenstrual syndrome (PMS) is to achieve relief from or significant decrease in symptoms, to limit discomfort, distress, and the disruption of personal relationships or usual activities. For most patients, carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

Nondrug Measures

- Try to avoid stress, develop effective coping mechanisms for managing stress, and learn relaxation techniques.
- If possible, participate in regular aerobic exercise.
- During the 7–14 days before the start of your menstrual period, reduce or eliminate intake of salt, caffeine, chocolate, and alcoholic beverages. Eating foods rich in carbohydrates and low in protein during the premenstrual interval also may reduce symptoms.

Nonprescription Medications

- Nonprescription medications and lifestyle modifications may not improve symptoms for all women, and it may take several months

to determine whether these therapies are working.

- Therapy with one nonprescription medication may improve only some of the symptoms; several medications may be needed for optimal symptom control. However, only add one agent at a time so that it is possible to determine which agent causes benefit or adverse effects.
- Follow the guidelines here for the agents that best control your symptoms:
 - Take 1200 mg of elemental calcium daily in divided doses. Calcium can be obtained from food or from supplements. Take no more than 500–600 mg at one time. Calcium may cause stomach upset (if this occurs, take with food) or constipation.
 - Take at least 600 IU of vitamin D daily.
 - Take 300–360 mg of magnesium pyrrolidone daily during the premenstrual interval only. Magnesium may cause diarrhea.
 - Take up to 100 mg of pyridoxine daily. Do not exceed this dosage; otherwise, neurologic symptoms caused by vitamin B₆ toxicity may occur.

When to Seek Medical Attention

- If you are taking vitamin B₆ and neurologic symptoms develop (e.g., a sensation of pricking, tingling, or creeping on the skin; bone pain; muscle weakness; or stinging, burning, or itching sensations), stop taking the vitamin and seek medical attention.
- If the PMS symptoms persist, or if they worsen, medical evaluation is suggested.

Toxic Shock Syndrome

Toxic shock syndrome (TSS) is a severe multisystem illness characterized by high fever, profound hypotension, severe diarrhea, mental confusion, renal failure, erythroderma, and skin desquamation. In the past, these symptoms and signs were recognized as affecting a relatively large number of young,

previously healthy, menstruating women. TSS is commonly divided into menstrual and nonmenstrual cases.

Menstrual TSS affects primarily young women between 13 and 19 years of age.⁵² Almost all cases of menstrual TSS have been associated with menstruation and tampon use, especially the use of high-absorbency tampons.⁵²

The decrease in cases of menstrual TSS has been attributed to several factors, including removal of superabsorbent tampons from the market; a change in the composition of tampons; an increased awareness of the recommendations to change tampons frequently and to alternate tampon and pad use; and FDA-required standardized labeling of tampons.⁵²

The strongest predictor of risk for menstrual TSS is the use of tampons, with risk increasing with tampon absorbency. For every 1 g increase in absorbency, the risk for TSS increases 34%–37%. Continuous uninterrupted use of tampons for at least 1 day during menses also has been shown to correlate with an increased risk for menstrual TSS. In addition, using tampons between menstrual periods (to manage vaginal discharge or nonmenstrual bleeding) can increase the likelihood of vaginal ulcers and the risk of TSS.⁵³ Besides tampons, TSS has been associated with the use of barrier contraceptives, including diaphragms, cervical caps and cervical sponges, IUC systems, and menstrual cups. The overall risk of TSS with menstrual cup use appears low, but limited evidence prevents comparison with other products, including tampons and diaphragms.⁵⁴

Pathophysiology of Menstrual TSS

Menstrual TSS is caused by the toxin-producing strains of *Staphylococcus aureus*.⁵⁵ TSS is an inflammatory immune response to the enterotoxins produced by these bacteria. Toxin-producing strains of *S. aureus* produce the superantigen toxin TSST-1. Most adults have a protective level of antibodies against the TSST-1 toxin. Younger people who lack this antibody protection and who become infected with a toxin-producing strain of *S. aureus* may develop TSS.⁵⁵

Four conditions promote toxin production: elevated protein levels, neutral pH,

elevated carbon dioxide levels, and elevated oxygen levels.⁵² During menses, menstrual blood provides an increase in protein and also increases vaginal pH to 7, or neutral pH. Tampon use may create the environment for development of TSS by introducing oxygen into the vagina; oxygen is trapped within the tampon, and higher-absorbency tampons carry more oxygen into the vagina.^{52,55} Oxygen is a critical factor for the production of TSST-1.⁵⁶ After the introduction of a tampon, the vagina takes hours to return to its anaerobic state, with elevated carbon dioxide levels. In addition, insertion and presence of tampons, IUC systems, and contraceptive sponges create microtrauma, which increases exposure of the toxins to the circulatory and immune systems. Exposure of immune cells to TSST-1 initiates the inflammatory cascade involving interleukin-1 and tumor necrosis factor. This inflammatory response results in the signs and symptoms of TSS.

Clinical Presentation of Menstrual TSS

By definition, menstrual TSS occurs within 2 days of the onset of menses, during menses, or within 2 days after menses. Prodromal symptoms, including malaise, myalgias, and chills, occur for 2–3 days before onset of the full-blown syndrome.⁵⁵ GI symptoms of vomiting, diarrhea, and abdominal pain typically occur early in the illness and affect almost all patients. After that, TSS evolves rapidly into high fever, myalgias, vomiting and diarrhea, erythroderma, decreased urine output, severe hypotension, and shock. Neurologic manifestations including headache, confusion, agitation, lethargy, and seizures also occur in almost all cases. Acute renal failure, cardiac involvement, and adult respiratory distress syndrome also are common.

Dermatologic manifestations are characteristic of TSS; both early rash and subsequent skin desquamation are required for a definitive diagnosis. The early rash often is described as a sunburnlike, diffuse, macular erythroderma that is not pruritic. Approximately 5–12 days after the onset of TSS, desquamation of the skin on the patient's face, trunk, and extremities (including the soles of the feet and the palms of the hands) occurs.

Prevention of Menstrual TSS

Menstrual TSS can be prevented almost entirely with use of sanitary pads instead of tampons during menstruation. Patients who use tampons can reduce the risk of developing TSS by following the guidelines in the box “Patient Education for Toxic Shock Syndrome.”

Women who have had TSS are at risk for recurrence. Rates of recurrence are reported as approximately 28%–64%.⁵³ Recurrence rates are lower for women who were treated with antibiotics during TSS. Prevention of TSS for these patients includes avoiding tampons, IUCs, diaphragms, cervical caps, and contraceptive sponges.

Assessment of Menstrual TSS: A Case-Based Approach

Obtaining prompt medical attention is an important aspect of care for patients with symptoms consistent with TSS. The health care provider can be alert for symptoms of TSS when patients seek nonprescription therapy for a severe “flu” with symptoms such as fever, vomiting, diarrhea, and dizziness, or when patients seek help for an unusual skin rash that occurs in conjunction with the previously described symptoms. If TSS is suspected, the patient should be advised to seek medical care immediately and to avoid use of NSAIDs for fever and myalgias, because these agents may advance the progression of TSS by increasing the production of tumor necrosis factor.

Patient Counseling for Menstrual TSS

Tampons are used by women of all ages during their reproductive years. Health care providers should counsel patients about the prevention of TSS as outlined in the box “Patient Education for Toxic Shock Syndrome.” In particular, patient counseling should emphasize the importance of washing the hands before inserting a tampon, which removes organisms causing TSS from the skin. Approximately 18%–36% of women report that they do not always change a tampon at least every 6 hours—another risk factor for TSS. Recommended preventive measures include changing tampons frequently, according to product instructions; alternating the use of tampons with the use of sanitary pads over a 24-hour period; and using the lowest-absorbency tampons

compatible with clinical needs. The health care provider should emphasize, however, that the risk for this condition is quite small. If a patient presents with early symptoms of TSS, she should be advised to remove the tampon or any barrier contraceptive device and to seek emergency medical treatment.

Patient Education for Toxic Shock Syndrome

The objective of self-treatment is to reduce the risk of developing toxic shock syndrome (TSS) associated with the use of tampons or contraceptive devices. For most patients, carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

- To reduce the risk of TSS to almost zero, use sanitary pads instead of tampons during your menstrual period.
- To lower the risk of TSS while using tampons, use the lowest-absorbency tampons compatible with your needs. Also, alternate the use of menstrual pads with the use of tampons (e.g., use pads at night) so that tampons are not used continuously for 24 hours.
- Change tampons 4–6 times a day and at least every 6 hours; overnight use should be for no longer than 8 hours.
- Wash your hands with soap before inserting anything into the vagina (e.g., tampon, diaphragm, contraceptive sponge, or vaginal medication). The bacteria causing TSS usually are found on the skin.
- Do not leave a contraceptive sponge, diaphragm, or cervical cap in place in the vagina longer than recommended; do not use any of these devices during menstruation.
- Do not use tampons, contraceptive sponges, or a cervical cap during the first 12 weeks after childbirth. It also may be best to avoid using a diaphragm.
- Read the insert on TSS enclosed in the tampon package, and become familiar with the early symptoms of this disorder.

When to Seek Medical Attention

- If you experience symptoms of TSS (high fever, pain or muscle

aches, a sunburn-like rash appearing after a day or two, weakness, fatigue, nausea, vomiting, and diarrhea), remove the tampon or contraceptive device immediately, and seek emergency medical treatment. If left untreated, TSS can cause shock and even death.

Key Points for Disorders Related to Menstruation

- Self-care is appropriate for otherwise healthy young women whose history is consistent with primary dysmenorrhea and who are not sexually active, and for patients previously diagnosed with primary dysmenorrhea. Adolescents with pelvic pain who are sexually active and thus at risk for PID and patients with characteristics indicating secondary dysmenorrhea or with persistent dysmenorrhea despite treatment with nonprescription agents should be referred for medical evaluation.
- NSAIDs are the drugs of choice for self-management of primary dysmenorrhea. These medications should be taken at the onset of or just before menses and should be used in scheduled doses for several days for optimal reduction in pain and cramping.
- The use of local topical heat also can provide relief from dysmenorrhea. Its analgesic effect has a faster onset than drug therapy, and it can add to the relief provided by an NSAID. Nonpharmacologic therapy may be especially useful for women who cannot tolerate or who prefer not to use drug therapy or whose symptoms do not respond to nonprescription NSAIDs.
- Premenstrual disorders should be distinguished from typical premenstrual symptoms and also from premenstrual exacerbations of other disorders, particularly mood disorders.
- Premenstrual disorder symptoms typically begin or intensify about a week before the onset of menses, peak on the 2 days

before menses, and resolve with menses initiation or shortly thereafter. A woman with a premenstrual disorder experiences a symptom-free interval during days 5–10 of her menstrual cycle.

- Mild to moderate PMS generally can be managed with self-treatment, including nondrug and/or nonprescription therapies; women with suspected PMDD are not candidates for self-care and should be referred to a primary care provider for appropriate diagnosis and management.
- Premenstrual disorder symptoms are chronic and, in most cases, will continue until menopause. Therefore, the cost of therapy, the possibility that a woman may become pregnant, and the likelihood of adverse effects from therapy are important considerations in selecting therapy.
- Use of calcium, pyridoxine, and chasteberry can be considered to reduce the symptoms of mild to moderate PMS. More severe PMS and PMDD symptoms may warrant referral to a primary care provider for further evaluation and/or prescription therapy.
- TSS has been linked to tampon use. To lower the risk for this potentially lethal disorder, women should use the lowest-absorbency tampons compatible with their needs and should alternate the use of sanitary pads with that of tampons over a 24-hour period.

Chapter 10: Prevention of Pregnancy and Sexually Transmitted Infections

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Unprotected sexual activity can result in unintended pregnancy and sexually transmitted infections (STIs), either of which can exact a high physical, psychological, and financial toll on affected persons. As discussed in this chapter, vaccines and properly used nonprescription contraceptive products or methods can reduce the risks of such adverse outcomes.

An estimated 45% of pregnancies in the United States are unintended.¹ The 2015–2017 National Survey of Family Growth (NSFG) found that approximately 65% of female subjects 15–49 years of age used contraception. Of the 35% not using contraception, approximately 8% were sexually active or at risk for unintended pregnancy.² Pharmacists can play an important role in improving rates of contraceptive use through counseling and dispensing as permitted by state law.

Although contraceptive use is prevalent, a continuing concern is the high risk of pregnancy and STIs in adolescents. The NSFG study also found that between 2011 and 2013, 40%–50% of teenagers had engaged in sexual intercourse.³ Of sexually active teenagers, about one fifth did not use contraception during their first sexual encounter.³ Low levels of contraceptive use in these teens may be related to a lack of knowledge and planning, denial, and infrequent or unpredictable intercourse. The teenage pregnancy rate in the United States is one of the highest among developed countries.³ However, as of 2017, birth rates for teenagers had reached historic lows for all age and ethnic groups.⁴ Adolescents also are particularly vulnerable to STIs, with many of the new STI infections each year occurring in young people 15–24 years of age.⁵ Risk factors for these infections include having multiple sexual partners, unprotected intercourse, an inherent biological susceptibility to infection, and financial and other barriers to health care utilization.^{5,6}

Women of older reproductive age also are at risk for unintended pregnancies. NSFG found that among women 35 years of age or older, 34% of pregnancies were unintended.¹ Postmenopausal women and older men in sexual relationships that are not mutually monogamous are additional groups at risk

for development of STIs.

The availability and relatively low cost of nonprescription contraceptive methods are important, especially for those who are unwilling or unable to access family planning services or use prescription contraceptives. Even if a prescription product is chosen as the primary contraceptive method, low-cost and low-risk nonprescription methods may be appropriate at different times during a person's life. In addition, the widespread accessibility of pharmacist-administered immunizations offers another opportunity for STI prevention.

Overview of Pregnancy and STIs

Pregnancy can result only when a viable egg is available for fertilization by a sperm. (See [Chapter 9](#) for discussion of the reproductive process.) Conception may occur during a 6-day window that begins 5 days before ovulation through the day of ovulation. The estimated risk of pregnancy from unprotected sexual intercourse during this period ranges from 5% to 45%, with peak risk occurring the day before ovulation.⁷ Pregnancy can occur despite contraceptive use if the product is used incorrectly or it fails, such as with condom breakage.

STIs are contracted through contact with infected genital tissues, mucous membranes, and/or body fluids. [Table 10–1](#) summarizes the major infections.^{6,8,9} Although STIs affect both sexes, women are more prone to reproductive consequences and related conditions, including pelvic inflammatory disease, chronic pelvic pain, pregnancy complications, malignancies, and infertility. This likelihood is possibly related to difficulties in diagnosis, lack of patient recognition of symptoms, and a higher probability of asymptomatic infection in female patients.¹⁰

Table 10–1 Sexually Transmitted Infections

Infection or Infectious Process (Cause: Pathogen Type)	Incubation Period	Symptoms	Diagnosis/Treatment	Complications	Congenital Transmission/ Neonatal Complications
Noncurable but Vaccine-Preventable Disease					

Table 10–1 Sexually Transmitted Infections

Infectious Infection or (Chlamydia Pathogen Type) Pathogen Type)	Incubation Period	Symptoms	Diagnosis/ Treatment	Complications	Congenital Transmission/ Neonatal Complications
Noncurable but Vaccine-Preventable Disease		Asx infections common;			
Genital warts (HPV ^a : DNA virus)	2–4 months (average)	Genital lesions, external condylomata, perianal, anal, penile, vulva, vagina, rectum, anus, perineum, mouth,	Colposcopy; serologic testing; molecular-based assays/cryoablation (chemical or physical); antivirals;	Cervical dysplasia/neoplasia, anogenital cancers, oropharyngeal cancer.	Yes/respiratory papillomatosis
Genital warts (HPV ^a : DNA virus)	2–4 months (average)	larynx, vagina, Acute, self-limited, mild cervix	antimetabolites; Serologic testing; antivirals	Cirrhosis, hepatocellular cancer	Yes
Curable Disease (hepatitis B virus: virus)	6 weeks-6 months	Acute, self-limited, mild	Serologic testing/antivirals	Cirrhosis, hepatocellular cancer	Yes
Curable Disease		Male: range from asx to urethritis, proctitis,			
Genital chlamydial infection (<i>Chlamydia trachomatis</i> : bacterium)	Several weeks	Males: range from asx to urethritis, proctitis, epididymo-orchitis, epididymitis, dysuria, discharge, postcoital bleeding, proctitis	NAAT/antibiotics	PID, ectopic pregnancy, infertility	Yes/neonatal conjunctivitis, pneumonia
Genital chlamydial infection (<i>Chlamydia trachomatis</i> : bacterium)	Several weeks	Females: range from asx to vaginitis discharge, postcoital bleeding, proctitis	NAAT/antibiotics	PID, ectopic pregnancy, infertility	Yes/neonatal conjunctivitis, pneumonia
Gonorrhea (<i>Neisseria gonorrhoeae</i> : bacterium)	Up to 14 days	pharyngitis, urethritis, purulent proctitis, discharge	Gram stain; culture; NAAT/antibiotics	Septic arthritis, perihepatitis, endocarditis, septic arthritis, PID, proctitis, ectopic pregnancy	Yes/sepsis, meningitis, arthritis, scalp abscesses, ophthalmitis, arthritis, scalp abscesses

Infection or Infectious Process (Cause: Pathogen Type)	Incubation Period	Symptoms	Diagnosis/Treatment	Complications	Congenital Transmission/ Neonatal Complications
		Female: Frequent vaginal discharge Male: mucopurulent urethral discharge Asx or mild clinical illness			
bacterium) Hepatitis C (hepatitis C virus ^b : virus)	8–9 weeks		Serologic testing; immunoassay; EIA; enhanced chemiluminescence immunoassay;	meningitis, PID, infertility, ectopic pregnancy Cirrhosis, hepato-cellular cancer	abscess; ophthalmia neonatorum Yes
			NAAT/giintestis; immunoassay; EIA; enhanced chemiluminescence immunoassay;		
Hepatitis C Nongonococcal (hepatitis C urethritis (men) virus ^c : virus) (various, including Chlamydia Neisseria gonorrhoeae Urethritidis (men) vaginalis, Mycoplasma genitalium Chlamydia trachomatis, Trichomonas vaginalis, Mycoplasma Syphilis sp.: bacteria) (Treponema pallidum: spirochete)	8–9 weeks	Asx or mild clinical illness Male: nonspecific urethritis, discharge, dysuria, Female: nonspecific urethritis, discharge, dysuria, pruritus	microscopy; NAAT; culture/antibiotics	Cirrhosis, hepato-cellular cancer Epididymitis, proctitis, proctocolitis, Reiter syndrome	Yes
	Varies		Gram stain microscopy; NAAT; culture/antibiotics	Epididymitis, proctitis, proctocolitis, Reiter syndrome	—
	Varies		Darkfield microscopy; treponemal and nontreponemal serologic tests/	Secondary syphilis: rash, lymphadenopathy Tertiary syphilis: cardiovascular, gummatous lesions	Yes/fetal death, prematurity, congenitalsyphilis
	3 weeks (average)	Primary syphilis: chancre	Darkfield microscopy; treponemal and nontreponemal serologic tests/	Gummatous lesions Lymphadenopathy CNS infection	Yes/fetal death, prematurity, congenitalsyphilis
Syphilis (Treponema pallidum: spirochete)	3 weeks (average)	Primary syphilis: chancre commonly asx Female: ~50% asx,	nontreponemal serologic tests/ antibiotics Microscopic examination of	Pregnancy: preterm labor, low birth weight	Yes
Trichomoniasis (Trichomonas vaginalis: protozoan)	Unknown (symptoms may appear within 28 days or years later)	Males: odorous, frothy green vaginal discharge 50% itching, dyspareunia,	vaginal fluids; Microscopic nucleic acid probe examination of test; PCR assay/ vaginal fluids; antibiotics nucleic acid probe test; PCR assay/		

Infection or Infectious Process (Cause: Pathogen Type)	Incubation Period	Symptoms	Diagnosis/ Treatment	Complications	Congenital Transmission/ Neonatal Complications
		pruritus, itching, green vaginal discharge, itching, After initial flu-like illness, bleeding OIs occur			
Noncurable Disease	days or years later)		antibiotics		
AIDS (HIV: virus)	Up to 10 years		Serologic antibody testing, NAAT/ antivirals; prophylaxis for OIs	OIs, malignancies, death	Yes, also transmitted via breast milk
Noncurable Disease					
Genital herpes (HSV-1, HSV-2: virus)	Up to 10 2-12 days	Asx or vesicular/ ulcerative lesions on mucous membranes	Serologic antibody testing; NAAT/ testing; PCR assay/ antivirals; prophylaxis for OIs	Disseminated infection, OIs, malignancies, hepatitis, meningitis/ encephalitis	Yes, also transmitted via breast milk
Genital herpes (HSV-1, HSV-2: virus)	2-12 days	Asx or vesicular/ ulcerative lesions on membranes	Culture; serologic testing; PCR assay/ antivirals	Disseminated infection, pneumonitis, hepatitis, encephalitis	Yes
Self-clearance of HPV may occur. ^a Compared with transmission through blood exposure, sexual transmission of hepatitis C is inefficient but may still occur, especially in persons with HIV infection.					

Key: AIDS = Acquired immunodeficiency syndrome; asx = asymptomatic; CNS = central nervous system; EIA = enzyme immunoassay;

^b Compared with transmission through blood exposure, sexual transmission of HIV = human immunodeficiency virus; HPV = human papillomavirus; HSV = herpes simplex virus; NAAT = nucleic acid amplification test; OI = opportunistic infection; PCR = polymerase chain reaction; PID = pelvic inflammatory disease.
 Key: AIDS = Acquired immunodeficiency syndrome; asx = asymptomatic; CNS = central nervous system; EIA = enzyme immunoassay;
 Source: References 6, 8, and 9.

HIV = human immunodeficiency virus; HPV = human papillomavirus; HSV = herpes simplex virus; NAAT = nucleic acid amplification test; OI = opportunistic infection; PCR = polymerase chain reaction; PID = pelvic inflammatory disease.

Source: References 6, 8, and 9.

Prevention of STIs and Pregnancy: Methods and Strategies

Vaccines for STI Prevention

Pharmacist-administered vaccination has become more common. Depending on state laws and regulations, vaccines for STI prevention may be available for administration in the pharmacy by protocol or without a prescription. States may limit the age range of persons for whom such vaccination is permitted, but in the absence of any regulatory or patient-specific barriers, availability of this service will increase the community vaccination rate for STIs.

Human Papillomavirus Vaccine

Human papillomavirus (HPV) is a virus that may be transmitted by sexual contact and is a major cause of cervical cancer and genital warts.^{6,11} Of the more than 120 different subtypes of HPV identified, HPV subtypes 16 and 18 are responsible for approximately 70% of cervical cancers. HPV subtypes 6 and 11 are responsible for benign cervical cell changes, genital warts, and laryngeal papillomas.¹² HPV also is responsible for a subset of vaginal, vulvar, penile, anal, and some head and neck cancers. HPV infection is the most common STI in the United States, with an estimated 14 million new cases annually.¹² The risk of infection is highest during the first few years after initiation of sexual activity.¹²

Three HPV vaccines have been developed: Cervarix (bivalent HPV vaccine; effective against HPV subtypes 16 and 18), Gardasil (quadrivalent HPV vaccine; for HPV subtypes 6, 11, 16, and 18), and Gardasil 9 (9-valent HPV vaccine; for HPV subtypes 6, 11, 16, 18, 31, 33, 45, 52, and 58).¹¹ Currently, only the 9-valent HPV vaccine is marketed in the United States and is approved for use in females 9–45 years of age to prevent precancerous or dysplastic lesions associated with specific HPV subtypes, genital warts and cervical, vaginal, vulvar, and anal cancers.¹³ It also is approved for use in males 9–45 years of age to prevent precancerous or dysplastic lesions associated with certain HPV subtypes, genital warts, and anal cancer.¹³

The current recommendation of the Advisory Committee on Immunization

Practices (ACIP) is for all 11- and 12-year-old adolescents to receive the applicable HPV vaccine, with vaccination supported in children as young as 9 years if necessary.¹¹ ACIP recommends a two-dose schedule, with immunizations given at 0 and 6–12 months, for adolescents up to 15 years of age who are initiating the vaccine. Those who initiate the vaccine series at age 15 years and older, as well as persons with certain immunocompromising conditions, should follow a three-dose schedule with immunizations at 0, 1–2 months, and 6 months.¹¹ A “catch-up” series is recommended for all persons through 26 years of age.¹¹ The vaccine works best before any HPV exposure from sexual contact, but previous sexual intercourse does not preclude vaccination with expected benefit.¹²

ACIP’s recommendation for HPV vaccine use has had a profound impact on HPV subtype prevalence in the United States. Comparison of data from a prevaccine time period with data collected from 2009–2012 showed a decline in HPV subtypes 6, 11, 16, and 18 among girls 14–19 years of age (11.5%–4.3%, respectively) and among women 20–24 years of age (18.5%–12.1%, respectively).¹⁴ Adverse effects of the vaccine may include irritation at the site of administration, self-reported malaise, and syncope. Because of the risk of syncope, particularly in younger girls, patients should be monitored for at least 15 minutes after administration of the vaccine.¹²

Hepatitis B Vaccine

Infection with the hepatitis B virus is associated with longterm complications such as hepatitis, cirrhosis, hepatic carcinoma, and death. The virus can be transmitted through contact with blood and other body fluids, and 79% of new infections occur in association with high-risk sexual behaviors or injection drug use.¹²

The hepatitis B vaccine is available as inactivated injectable formulations, with an administration schedule of a three-dose series of injections at 0, 1, and 6 months or a two-dose series of injections at 0 and 1 month.^{12,15} The two-dose series is approved only for the HepB-CpG vaccine, which uses a different adjuvant from the traditional aluminum adjuvant vaccines and is available for adults 18 years of age and older.¹⁵ Recommended as a routine immunization for all infants starting at birth, hepatitis B vaccination also is provided to children and adolescents who did not receive the vaccine as infants or who did not complete the series. Adults who desire protection from hepatitis B

infection or those who meet risk criteria and who were not previously vaccinated should also receive the series. Candidates for the vaccine due to sexual exposure include partners of hepatitis B–infected persons, those not in long-term mutually monogamous sexual relationships, those in need of evaluation or treatment for a STI, and men who have sex with men. Other potential candidates include injection drug users; health care and emergency response personnel; patients with diabetes, end-stage renal disease, human immunodeficiency virus (HIV) infection, hepatitis C infection, or liver disease; international travelers; and residents of correctional facilities or facilities for developmentally disabled persons.¹⁵

Contraception for Pregnancy and STI Prevention

The goal of contraceptive use is to prevent unintended pregnancy and STIs with minimal adverse effects. No method of birth control except abstinence is 100% effective, and contraceptive choices may change during a lifetime.

The effectiveness of a contraceptive method in preventing pregnancy is reported in two ways: the accidental pregnancy rate in the first year of *perfect* use (method-related failure rate) and the rate in the first year of *typical* use (use-related failure rate). [Table 10–2](#) summarizes effectiveness data for various contraceptive methods.^{16–20} The pregnancy rate with perfect use is difficult to measure and indicates the method’s theoretical effectiveness. Perfect use assumes accurate and consistent use of the method every time intercourse occurs. The more realistic rate with typical use takes into account pregnancies that may have occurred because of inconsistent or incorrect use of the method. Reported use-related failure rates vary, depending on the population studied. Decreased coital frequency and declining fertility in older users may contribute to increased effectiveness rates in this population. Effectiveness also increases the longer an individual uses a particular method.¹⁸

Table 10–2 Failure and Use Rates for Various Contraceptive Methods

Method	Accidental Pregnancy Rate in First Year of Use (%)		% of Women Using Method ^c
	Typical Use ^a	Perfect Use ^b	
No method at risk for pregnancy	85	85	10.5

Method	Accidental Pregnancy Rate in First Year of Use (%)		% of Women Using Method ^c
	Typical Use ^a	Perfect Use ^b	
Withdrawal	20	4	7.1
Fertility awareness-based methods	15	–	1.9
Calendar method	15–19	3	–
Symptothermal method	2	0.4	–
Lactational amenorrhea method (first 6 months after giving birth)	2–3	0.5	
Standard days method	12	5	–
TwoDay Method	14	4–6	–
Natural Cycles app	8	1	–
Spermicides (foam, creams, gels, vaginal suppositories, vaginal film)	21	16	<0.2
Contraceptive sponge	<i>Parous women: 27</i>	<i>Parous women: 20</i>	<0.2
	<i>Nulliparous women: 14</i>	<i>Nulliparous women: 9</i>	
Male condom (without spermicide)	13	2	13
Female condom (without spermicide)	21	5	<0.2
Prescription methods (excluding diaphragm, cervical cap)	0.2–9	≤0.6	42.5
Sterilization (male/female)	≤0.5	≤0.5	11.6

^a Among typical couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

^b Among typical couples who initiate use of a method (not necessarily for the first time) and who use it consistently and correctly, the percentage who experience an

accidental pregnancy during the first year if they do not stop use for any other reason.

^c Percentage of female users 15–44 years of age.

Source: References 16–20.

The most effective way to avoid contracting a STI is either to abstain from risky sexual activity or to be involved in a longterm mutually monogamous sexual relationship with an uninfected partner.⁶ In the absence of those options, preventive strategies ([Table 10–3](#))^{6,10} in conjunction with use of selected contraceptives may provide the best method for reducing risk of infection ([Figure 10–1](#)).^{6,10,20–24}

Table 10–3 Prevention Strategies for Sexually Transmitted Infections

- Abstain from sexual activity.
- Avoid intercourse with a known infected partner.
- Avoid intercourse with an individual having multiple sex partners.
- Use a new condom with each episode of anal, oral, or vaginal intercourse.
- Seek a mutually monogamous relationship with an uninfected partner.
- Discuss partner's past sexual experiences.
- Examine partner for genital lesions.
- Practice genital self-examination.
- Avoid sexual activity involving direct contact with blood, semen, or other body fluids.
- Avoid sharing sexual devices that come in contact with semen or other body fluids.
- Choose safe and effective methods (e.g., mechanical barriers) to reduce the risk of STIs (consider adding more effective methods of pregnancy prevention when necessary).
- Avoid sexual activity if signs/symptoms of an STI are present.
- Consider vaccination for persons at high risk for a vaccine-preventable STI (e.g., HBV or HPV infection).

Key: HBV = Hepatitis B virus; HPV = human papillomavirus; STI = sexually transmitted infection.

Source: References 6 and 10.

The acceptability of any given contraceptive method is vital for correct and

consistent use of that method. Factors that affect acceptability include the user's religious beliefs and future reproductive plans, product effectiveness, partner's preference and support, degree of spontaneity permitted, ease of use, product accessibility, and cost. To help patients make informed decisions, health care providers should be cognizant of each method's safety, including potential adverse effects on future fertility and on the fetus, if unintended conception does occur, and the effectiveness, accessibility, and relative cost of different contraceptive methods. The algorithm in [Figure 10–1](#) can assist the health care provider in making appropriate contraceptive recommendations.

Nonprescription Contraceptive Products

Male Condoms

Condoms, also known as *rubbers*, *sheaths*, *prophylactics*, *safes*, *skins*, or *pros*, are the most important barrier contraceptive devices that help protect against STIs.¹⁸ Male condoms are available in several materials: latex, polyurethane, polyisoprene, and lamb cecum (natural membrane or skin) ([Table 10–4](#)).

Table 10–4 Selected Male Condoms	
Type	Trade Name
Synthetic, nonlatex condoms	Durex Avanti Bare RealFeel (polyisoprene), Trojan Supra (polyurethane), Lifestyles Skyn (polyisoprene)
Natural membrane condoms	Trojan Naturalamb (lamb cecum)
Latex condoms	Beyond Seven, Billy Boy, Crown, Durex, Kimono, LifeStyles, One, Sir Richard's, Trojan

Latex condoms come in various sizes, colors, styles, shapes, and thicknesses. Other features include reservoir tips, ribs, studs, spermicide coating with nonoxynol-9, and lubrication. Of note, latex condoms are degraded by oil-based lubricants. The list price at a major pharmacy chain for latex condoms is \$0.18–\$1.08 each.²⁴ Latex condoms also help protect against STIs.²⁰ Polyurethane condoms conduct heat well, are available prelubricated, are not subject to degradation by oil-based products but are not as elastic as latex

condoms.²⁵ Another form of synthetic condom is made of polyisoprene, which is more elastic than polyurethane but can be damaged by oil-based lubricants. Although synthetic and latex condoms are thought to provide similar protection against STIs, prevention of STIs with synthetic condoms has not been well studied. The U.S. Food and Drug Administration (FDA) labeling restricts synthetic condom use to latex-sensitive or latex-allergic persons.²⁰ At a cost of \$0.67–\$1.86 each, polyurethane and polyisoprene condoms are more expensive than latex condoms.²⁴

Lamb cecum condoms are labeled only for pregnancy prevention, because the presence of pores in the membrane may allow passage of viral organisms, including HIV and hepatitis B virus.²⁰ These condoms conduct heat well, are very strong, and are not degraded by oil-based lubricants. With a price of approximately \$2.55 each, these condoms also are more expensive than latex condoms.²⁴

FDA regulates condoms as medical devices, and they must meet performance standards for strength and integrity. The true incidence of condom breakage is unknown, and breakage rates from studies vary widely, ranging from zero to 22%.²⁶ The overall use-related failure rate for condoms is approximately 13 pregnancies per 100 women during the first year of use ([Table 10–2](#)). In some studies, a limited group of patients reported multiple instances of breakage, indicating that breakage may be related as much to the individual user as it is to manufacturing defects. Behaviors that have been associated with an increased risk of condom breakage are (1) incorrect placement of the condom/ failure to squeeze air from the receptacle tip; (2) use of an oil-based lubricant with latex condoms; (3) reuse of condoms; (4) longer duration or increased intensity or frequency of coitus; (5) previous history of condom breakage or slippage; (6) history of STI; (7) contact with sharp objects; (8) self-reported problems with fit of a condom; (9) impaired or intoxicated state, from drugs or alcohol, in either partner; and (10) brief acquaintance, less than 1 month, with the sexual partner.^{20,26–29} One study found a decreased incidence of breakage with continued use, indicating that correct technique may improve with experience.²⁶ The benefit of using additional lubrication with lubricated condoms is unclear. One study found that use of additional lubricant increased the risk of condom slippage. Another study, however, found that use of an additional water-based lubricant was associated with decreased breakage rates but caused no increase in condom slippage rates.²⁸ A review of comparative studies found that nonlatex synthetic condoms had a

significantly higher breakage rate than that with latex condoms.^{25,30,31} Two studies also reported a significantly higher pregnancy rate with use of nonlatex condoms compared with latex condoms.^{31,32} Accordingly, nonlatex condoms should be reserved for use by persons with intolerance to latex condoms.

Studies support the finding that consistent use of condoms protects against trichomoniasis, bacterial vaginosis, and gonorrhea infections in women, and against syphilis and chlamydial, HPV, and herpes simplex virus infections in both men and women.²⁰ Nonoxynol-9–coated (spermicide-coated) male condoms are no more effective than untreated condoms at preventing STIs and have not been shown to be more effective in pregnancy prevention.³³ Use of nonoxynol-9-treated condoms is discouraged because of the potential risk of irritation from the spermicide in both men and women, resulting in possible increased risk of infection.²⁰

Proper use of condoms is essential to their effectiveness in preventing pregnancy and STIs ([Table 10–5](#)). For example, a man using a polyurethane condom should be advised that it is not as elastic as the latex condom and will not fit as snugly. In addition, condoms without a reservoir require that a space be left at the condom tip.

Table 10–5 Usage Guidelines for Male Condoms

- Use only condoms that are fresh (not previously opened), that are within their expiration date, and that have been stored in a dry, cool place (not a wallet or vehicle glove compartment).
- Do not attempt to test the condom for leaks before using; this maneuver will weaken the condom.
- Be aware that long fingernails or jewelry may easily tear condoms.
- As shown in drawing A, unroll the condom onto the erect penis before the penis comes into any contact with the vagina. If you start to put the condom on incorrectly, with the exterior touching the penis, discard that condom and use a fresh one. (Note: Pre-ejaculate secretions may contain sperm.)
- If you are not using a reservoir-tipped condom, leave one-half inch of space between the end of the condom and the tip of the penis by pinching the top of the condom as you unroll it (drawing B). This method leaves space for the ejaculate (drawing C) and decreases the risk of breakage.
- If your partner has vaginal dryness, use additional lubrication, if desired. This step will help decrease the risk of tears and breakage. Use only water-based lubricants; oil-based

lubricants weaken latex condoms and increase the chance of breakage. Spermicidal agents may be used as lubricants with condoms (Table 10–8), and the combination may increase contraceptive effectiveness.

- After ejaculation, withdraw the penis immediately. To prevent the condom from slipping off, hold on to the rim of the condom as you withdraw.
- Check the condom for tears and then discard in a trash can, not a toilet.
- If a tear or break occurs, immediately insert spermicidal foam or jelly containing a high concentration of spermicide into the vagina. Do not use suppositories or a vaginal film in these cases, because the delay time for dissolution may decrease the product's efficacy. Your partner should not douche at this time, because any sperm that are present may be forced into the cervical canal. Consider use of emergency contraception as soon as possible and within 72–120 hours after unprotected intercourse if pregnancy is a concern.

Prelubricated condoms are a good choice when lubrication is desired. Additional lubrication for use with any latex condom should be selected from products that do not impair the strength and integrity of the condom (Table 10–6).

Table 10–6 Selected Lubricants/Products That Are Safe or Unsafe to Use With Latex Condoms

Safe	Unsafe
Contraceptive foams/gels	Topical oils (e.g., baby oil, mineral oil, massage oil)
Water-based personal lubricants, such as K-Y Jelly or Astroglide	Edible oils/fats (e.g., olive, peanut, corn, canola, and safflower oils; butter; margarine)
Silicone-based lubricants, such as Astroglide X, Replens lubricant	Hemorrhoidal ointments
Glycerin (USP)	Petroleum jelly (e.g., Vaseline)
Water	Vaginal creams (e.g., Monistat, others)
Saliva	Hand and body lotions; suntan lotions

Source: Reference 20.

Packaged condoms should be kept in their sealed packages until time of use and protected from light and excessive heat, which can rapidly compromise the integrity of the condom material. FDA requires that condoms be labeled with an expiration date or date of manufacture. The shelf life of packaged condoms under optimal conditions is 3–5 years. Condoms showing signs of discoloration, brittleness, or stickiness should be discarded, even if they are within their expiration date.

The most frequent complaints about condoms are decreased sensitivity of the glans penis, resulting in decreased sexual pleasure for the man, and sensitivity to the condom material. The use of very thin or ridged condoms, nonlatex synthetic condoms, or natural membrane condoms in a monogamous relationship with a partner screened for STI exposure may alleviate the problem of decreased sensitivity.

Contact dermatitis caused by latex allergy can occur in the male or female partner and may be characterized by immediate localized itching and swelling (urticarial reaction) or by a delayed eczematous reaction. The sensitizers in latex condoms are usually antioxidants or accelerators used in processing the rubber. In persons with severe sensitivity, the reaction may include systemic symptoms. Spermicide-treated condoms may be associated with enhanced latex allergy, or the spermicide may be the cause of the sensitivity reactions.³⁴

For most people, condoms are an effective, acceptable, inexpensive, safe, and nontoxic method of birth control. Given the range of condoms available, men should be encouraged to try a different style or brand if they are dissatisfied with a condom used previously. Before recommending a latex condom, health care providers should assess for latex allergy. Ways to assess for possible latex allergy include asking if the patient has had any reactions to latex gloves, for example, or has experienced any reactions when inflating balloons. In patients with an established sensitivity to latex products, an alternate type of condom should be recommended. Some men and women may be sensitized to components of the lubricant or spermicide. Because manufacturers use different processes, changing brands or using a condom without spermicide may resolve the problem.²⁰ If switching brands does not eliminate the irritation, the man may use nonlatex synthetic condoms. Natural skin condoms also may be used if their limitations in preventing STIs are recognized.

Other uses for barrier methods include prevention of STI transmission through oral sex. A dental dam (square piece of latex or silicone used to cover the

vagina or anus during oral sex) or a condom cut lengthwise and spread open also may be used for this purpose.³⁵ Intact condoms may be used on the penis during oral sex.

Female Condoms

A female condom is another nonprescription contraceptive product. The only female condom available is a second-generation female condom known as the FC2, which is made of nitrile, a synthetic latex.³⁶ The female condom consists of an outer ring, a sheath or pouch that fits over the vaginal mucosa, and an inner ring that secures the sheath by fitting like a diaphragm over the cervix. The female condom is designed for one-time use only and, at a cost of \$2.00 each, is more expensive than the latex male condom.²⁴

The breakage rate for the female condom has been lower than that for latex male condoms, but slippage rates may be higher, especially with initial use.²⁷ Although specific data regarding failure rates for the FC2 were not available when it was first released on the market, it was comparable to the first-generation female condom, the FC1.³⁷ The extrapolated annual failure rate for the FC1 is 21% for all users and 5% for perfect users (**Table 10–2**).^{21,37} A more recent study comparing three different female condom brands available outside the United States with the FC2 reported a failure rate of 3.43% for the FC2, confirming its similarity in effectiveness to the FC1.³⁸ The female condom is an effective barrier to sexually transmitted bacteria and viruses and is similar in efficacy to latex male condoms in decreasing the risk of STIs.²²

Table 10–7 provides instructions for proper use of the female condom.³⁶ Skills in correct insertion of the female condom improve with practice and continued use.³⁹ The condom may be inserted up to 2 hours before intercourse, but it is effective immediately on insertion.³⁶ Fresh condoms can be stored at room temperature in their unopened packages. Before inserting the female condom, the woman should ensure that the product is within its expiration date.

Table 10–7 Usage Guidelines for Female Condoms

- Remove the condom from the package. One end of the condom is closed to form a pouch, as shown in drawing A.
- Gently rub the sides together to evenly distribute the lubricant inside the pouch. If needed,

add additional lubrication at this point.

- Add a drop of lubricant on the outside of the pouch to improve the ease of insertion if needed. Oil- or water-based lubricants can be used with this condom.

To place the pouch properly, grasp the inner ring between the thumb and middle finger of one hand. Place the index finger on the sheath between the other two fingers. (See drawing B.)

- Be careful that jewelry or sharp fingernails do not tear the condom.
- Squeeze the inner ring, and with your other hand, spread the lips of the vagina. Then insert the squeezed condom into the vagina as far as possible. (See drawing C.)
- Be sure that the inner ring is placed beyond the pubic (pelvic) bone, that the pouch is not twisted, and that the outer ring is outside the vagina, as shown in drawing D.
- During intercourse, make sure that the penis enters the vagina inside the pouch and that the outer ring remains outside the vagina.
- If desired, add more lubricant during intercourse, without removing the condom.
- Until the couple is comfortable using the female condom, it is recommended that the penis be inserted by hand into the vagina.
- If the female condom is slipping out of the vagina during intercourse or if the outer ring is going into the vagina, stop intercourse. Remove the female condom and insert a new condom.

Remove the pouch before standing by twisting the outer ring and pulling gently. (See drawing E.)

- Discard the used condom in a trash can, not a toilet.
- Insert a new condom for each act of intercourse.
- Do not use a male condom with the female condom. The increased friction could cause displacement of the female condom.

Source: Reference 36.

The most common complaints about the female condom are vaginal irritation and increased noise (“squeaking”). Additional lubrication may resolve those problems. Some women may experience decreased sensation or even discomfort, which is caused by the outer ring during intercourse.

The female condom provides a method for women to protect themselves against pregnancy. Compared with vaginal spermicides, the female condom can be inserted much earlier before intercourse and is less messy to use.

However, some women may find the female condom cumbersome and unattractive. The female condom should not be used together with the male condom. Use of both products together may cause friction, thereby increasing the risk of breakage for either product.³⁶

Vaginal Spermicides

Vaginal spermicides use surface-active agents to immobilize and kill sperm. With gels and foams, the spermicide vehicle also acts as a physical barrier against sperm. The effective spermicides include nonoxynol-9, octoxynol-9, and menfegol, but in the United States, all products contain nonoxynol-9 (Table 10–8). Vaginal spermicide products differ in their application method, onset, and duration of action (Table 10–9). The price range of vaginal spermicides ranges is \$0.71–\$1.44 per dose.²³

Table 10–8 Selected Nonprescription Vaginal Spermicides Containing Nonoxynol-9	
Product Type	Trade Name
Spermicidal foams	VCF Vaginal Contraceptive Foam 12.5%
Spermicidal gels/jellies	Options Conceptrol Gel 4%, 100 mg VCF Vaginal Contraceptive Gel 4% Options Cynol II Extra Strength Vaginal Contraceptive Gel 3%, 150 mg
Spermicidal suppositories	Encare Vaginal Contraceptive Inserts 100 mg
Spermicidal film	VCF Vaginal Contraceptive Film 28%
Spermicidal sponge	Today Contraceptive Sponge 1000 mg

Vaginal gels (“jellies”) provide additional lubrication and are safe to use with latex condoms. For convenience, applicators may be prefilled before use. Prefilled unit-dose applicators are also available for some products. Vaginal foams distribute more evenly and adhere better to the cervical area and vaginal walls but provide less lubrication than jellies. A new canister should always be available, because it is difficult to determine when the canister is

nearly empty.

Vaginal suppositories are solid or semisolid dosage forms that are activated by moisture in the vaginal tract. Incomplete dissolution of the suppository may result in an unpleasant, gritty sensation. Although vaginal suppositories do not require refrigeration, in warmer climates, refrigeration may be desirable to prevent softening.

Vaginal contraceptive film contains nonoxynol-9 in paper-thin, 2-inch-square sheets. The film is activated by vaginal secretions. One film is used for each act of intercourse. The practice of inserting the film by placing it over the penis should be avoided, because this method does not ensure proper placement and does not allow adequate time for dissolution. In one comparison of spermicide formulations, the film was rated the most difficult to use but the least messy.⁴⁰ Similarly designed vaginal films for cleansing or lubrication do not contain spermicide and should not be used for contraception. Patients should be advised to verify that they are using the correct vaginal film product if they desire contraception.

Spermicides used alone carry a relatively high rate of typical usage-related failure among first-year users ([Table 10–2](#)). A review of clinical trials found similar pregnancy rates for products containing 100–150 mg nonoxynol-9 per dose.⁴¹ A gel containing 52.5 mg nonoxynol-9 per dose, which is not available in the United States, was significantly less effective at preventing pregnancy than the higher-dose formulations.⁴¹ Efficacy improves greatly if spermicides are used with barrier methods such as diaphragms, cervical caps, or condoms.

Although nonoxynol-9 can inactivate many sexually transmitted pathogens in vitro, clinical studies do not support a protective effect of vaginal spermicides against STI transmission.^{21,42} Higher rates of genital lesions, especially in frequent users, have been reported, raising concerns about an increased risk for STI transmission.^{21,42} In 2007, FDA ruled that vaginal spermicide products must carry a label stating that the product does not protect against HIV and other STIs.⁴² In persons with known risk factors for STIs, spermicides should be recommended only in conjunction with condom use.

[Table 10–9](#) provides guidelines for the proper administration of vaginal spermicides.^{21,43,44} With use of any vaginal spermicide, a woman should delay douching for at least 6 hours after intercourse. Although allergic reactions are rare, either partner may experience such reactions to spermicides. Couples

engaging in oral–genital sex may find the taste of some products unpleasant. Frequent use or use of high-concentration products may lead to irritation of or damage to vaginal and cervical epithelium,⁴² which may be associated with an increased risk for STIs. Despite initial concerns about a possible association between spermicide use and birth defects or miscarriage should an unintended pregnancy occur, current data do not support an increased risk of either attributable to spermicides.⁴⁵

Table 10–9 Administration Guidelines for Vaginal Spermicides

Dosage Form	Application Method	Onset/Duration of Action	Application Time Before Intercourse	Reapplication Requirements
Vaginal gel alone	Insert full dose near cervix.	Immediate/1 hour after application	Up to 1 hour	Reapply for each coital act.
Vaginal gel used with diaphragm/ cervical cap	Fill barrier device one-third full with gel and place it near cervix. Leave barrier in place for at least 6 hours after intercourse.	Immediate/ <i>diaphragm</i> : 6 hours; <i>cervical cap</i> : 48 hours	Up to 1 hour	<i>Diaphragm</i> : for each coital act that occurs within 6 hours of initial insertion of device, reapply spermicide without removing device; for coitus after 6 hours of initial insertion, remove and wash device, fill with new spermicide, and re-insert device.
				<i>Cervical cap</i> : remove and wash device; then reapply spermicide for each coital act that occurs 48 hours after initial insertion of device.
Vaginal foam	Insert full dose near cervix.	Immediate/1 hour	Up to 1 hour	Reapply for each coital act.
Vaginal suppository	Insert suppository	10–15 minutes/1 hour	10–15 minutes	Reapply for each coital act.

Dosage Form	Application Method	Onset/Duration of Action	Application Time Before Intercourse	Reapplication Requirements
	near cervix.			
Vaginal contraceptive film	Drape film over fingertip; place film near cervix.	15 minutes/3 hours	15 minutes	Reapply for each coital act. Insert at least 15 minutes but not more than 3 hours before intercourse. If 3 hours have elapsed from the time of insertion before intercourse, insert a new film.
Vaginal contraceptive sponge	Moisten with tap water; insert convex side against cervix.	Immediate/24 hours	Can be inserted up to 24 hours before intercourse.	Leave in for >6 hours after intercourse, but no longer than 30 hours total; use polyester loop to facilitate removal.

Source: References 21, 43, and 44.

The relatively low effectiveness rate for spermicides when used alone is their major disadvantage. Studies suggest, however, that simultaneous use of condoms and spermicides provides higher effectiveness rates than those for spermicides alone.¹⁷ Their ready availability and ease of use make spermicides a good choice for women who need a backup method. Spermicides are not recommended for women with vaginal anatomic abnormalities that would prevent the proper placement of the spermicide near the cervical opening. Product selection can be based on patient preference and specific product characteristics.

Contraceptive Sponge

The contraceptive sponge marketed as the Today Sponge is a small, circular,

disposable sponge made of polyurethane permeated with the spermicide nonoxynol-9. The sponge is believed to act as a contraceptive by serving as a mechanical barrier, providing a spermicide, and absorbing semen. The price range of contraceptive sponges is \$5–\$8 per sponge.²⁴

In two large trials, the failure rate for the contraceptive sponge ranged from 17.4 to 24.5 pregnancies per 100 women in the first year of use.⁴⁶ Women who had given birth previously (parous women) had a significantly higher pregnancy rate while using the sponge compared with women who had never given birth (nulliparous women). That finding may be related to poor fit in women who have delivered vaginally. If the sponge becomes dislodged during intercourse, its efficacy may be decreased.

The contraceptive sponge does not protect against STIs. One study found an increased risk of HIV infection in women with frequent sponge use, possibly because of an increased incidence of vaginal ulceration from the spermicide.²³

A woman must be able to locate her cervix with a reasonable degree of comfort and competence for correct placement of the sponge. **Table 10–9** provides instructions for proper use. The sponge has a loop attached to the convex side to facilitate its retrieval. Some women have difficulty removing the sponge, and it has been known to fragment on removal. The sponge may be inserted up to 24 hours before intercourse but must remain in place for 6 hours after intercourse. The sponge should be stored in its unopened package in a cool place and used before its expiration date.

Some adverse effects, such as vaginal dryness, have been reported with use of the contraceptive sponge. A well-recognized association is the development of toxic shock syndrome (TSS), although the incidence is low.²² Women should take special care to wash their hands before inserting the sponge. The sponge should not be used during menstruation or in the first 6 weeks after giving birth. Use should not exceed the maximum recommended retention time of 30 hours. Women also should be advised to make sure the entire sponge is removed, because fragments left in the vagina may serve as a source for infection.

The contraceptive sponge is convenient, safe, and portable. Contraindications to its use include spermicide sensitivity, anatomic abnormalities of the vagina, and a history of TSS. The contraceptive sponge should not be routinely recommended to parous women, because possible problems with adequate

cervical coverage may lead to increased risk of pregnancy.

Emergency Contraception

Emergency contraception (EC) involves the use of hormones in the form of oral tablets or a nonhormonal copper intrauterine contraceptive (IUC) to prevent pregnancy as soon as possible after unprotected intercourse and up to 3–5 days after unprotected sexual intercourse based on product labeling and current practice.⁴⁷ Hormones used in EC products may include progestin (synthetic progesterone) as a single agent, estrogen in combination with a progestin, or a selective progesterone receptor modulator. The progestin commonly found in the EC formulations is levonorgestrel. Nonprescription and prescription oral tablet formulations are available. This section focuses on nonprescription progestin-only products.

EC products should be recommended for girls and women of reproductive age who have had recent unprotected intercourse, who experienced method failure such as condom breakage, or who desire advance provision in the event of a need for EC.^{17,47} Some women may be seeking EC in the case of sexual assault. In addition to providing EC for immediate use, pharmacy staff should refer the patient to primary care providers who can evaluate her for STIs and report the incident to the authorities as required by state law.

EC products reduce the expected number of pregnancies by 52%–100% for levonorgestrel users.⁴⁷ The efficacy of EC is primarily due to the suppression of ovulation. Other possible mechanisms of action are those involving interference with transport of sperm or egg, including thickening of cervical mucus.^{16,47} Over-the-counter EC products will not affect an implanted embryo or increase the risk of malformations in the event of pregnancy.⁴⁷

Current nonprescription options that include levonorgestrel-containing tablets, available as single-tablet formulations in the generic branded products are Aftera, EContra EZ, My Way, New Day, Opcicon One-Step, Plan B One-Step, Preventeza, React, and Take Action.⁴⁷ Progestin-only products cost between \$40 and \$50 for single-incident use.²⁴ Nonprescription products each contain 1 tablet of levonorgestrel 1.5 mg labeled to be taken as a single dose within 72 hours after unprotected intercourse or contraceptive failure. Studies have shown effectiveness up to 120 hours after intercourse, although efficacy declines with more time after coitus.⁴⁷ Therefore, women presenting for EC within 120 hours of unprotected sex could be offered nonprescription EC

products or referred to their primary care provider for ulipristal acetate or insertion of the copper IUC. Body weight may influence the effectiveness of the levonorgestrel, which may not be as effective in patients with a body mass index (BMI) of 26 kg/m² or greater.⁴⁷ Alternative EC products available by prescription also may be an option ([Table 10–10](#)).⁴⁷

Table 10–10 Prescription Emergency Contraceptives Available			
Product Name	Dosage	Timing for Use	BMI and Effectiveness
Ulipristal acetate (ella)	30 mg	Within 120 hours post coitus	May start to lose effectiveness at BMI of 30, may become ineffective at BMI of 35; should not be with-held from patient on the basis of her BMI
Copper IUC (ParaGard T380A)	n/a	Off-label use; within 120 hours post coitus	No issue with BMI
Estrogen and progestin (combined regimen)	Varies: Ethinyl estradiol 100–120 mcg and levonorgestrel 0.5–0.6 mg (amount per dose; take 2 doses separated by 12 hours)	Off-label use; within 72 hours, although studies suggest up to 120 hours post coitus	No information

Key: BMI = Body mass index; IUC = intrauterine contraceptive; n/a = not applicable.

Source: [Reference 47](#).

The most common adverse effects reported with oral EC use are nausea and vomiting.^{16,47} Nausea occurs in approximately 25% of women using progestin-only products. Vomiting occurs in approximately 5% of progestin-only EC users. An antiemetic usually is not necessary for progestin-only EC but may be recommended 60 minutes before each dose with use of combination oral contraceptive regimens.^{16,47} If the patient vomits within 1–2 hours after taking the dose, she should repeat the dose.^{16,47} Headaches, breast tenderness,

menstrual changes, and dizziness also have been reported by users.⁴⁷ **Table 10–11** provides patient counseling points and information about levonorgestrel EC products.

Table 10–11 Counseling Points for Emergency Contraception (Levonorgestrel)

- Identify whether patient has had recent unprotected sex within the past 120 hours or is at risk for unprotected sex and does not want to get pregnant.
- Identify whether patient is an appropriate candidate for EC using nonprescription products.
- Explain how to take EC products: Aftera, EContra EZ, My Way, New Day, Opcon One-Step, Plan B One-Step, Preveneza, React, or Take Action is given as a single dose and should be taken as soon as possible. EC is most effective when the product is taken as soon as possible after unprotected intercourse. The method is effective when the product is taken up to 120 hours after unprotected intercourse, although package labeling states within 72 hours.
- Recommend an antiemetic for women using combination oral contraceptives for EC.
- If the woman has a BMI of 26 or greater, explain that the effectiveness of the nonprescription EC products may be reduced, but do not withhold product. Alternative options could include a prescription for ulipristal or referral to a primary care provider for insertion of the copper IUC.
- Discuss adverse effects of EC, which may include a change in menstrual cycle depending on when the product is used. Patients may have their next menstrual period early or late or experience no change. If menstruation has not occurred more than 21 days after use of an EC product, the patient should take a pregnancy test.
- Emphasize that EC is not to be used as a regular contraceptive method.
- Recommend that a sexually active woman begin using regular contraception after taking an EC product. Barrier methods should be used with each subsequent act of intercourse during rest of the current menstrual cycle. Hormonal contraceptive methods may be started with the next menses or may be started the day after levonorgestrel EC, with 7 days of a backup contraceptive method.
- Explain that EC products do not protect against STIs.
- Explain that EC is not 100% effective. Recommend using a pregnancy test if the menstrual period is more than 21 days late.
- Recommend a longer-term method of contraception if patient is using EC multiple times a month. Although such frequent usage of EC is safe, these products are not intended to be used in this way. A longer-term contraceptive method will provide better protection against pregnancy.
- Provide written instructions.

Key: BMI = Body mass index; EC = emergency contraception; IUC = intrauterine contraceptive; STI = sexually transmitted infection.

Source: References 16 and 47.

Patients presenting with pregnancy concerns between 5 and 7 days after unprotected intercourse should be referred to a primary care provider for possible insertion of a copper IUC.¹⁶ Although a copper IUC usually is placed up to 5 days after unprotected intercourse, the device can be inserted up to 8 days after intercourse if ovulation is known to have occurred more than 72 hours after intercourse.¹⁵ Therefore, if intercourse occurred 3 days before ovulation, the patient could potentially still have an IUC placed up to 5 days after ovulation, although in practice it is usually placed up to 5 days after unprotected intercourse.¹⁶

Fertility Awareness–Based Methods

Contraceptive methods that do not use a chemical or a barrier to prevent conception include calendar methods, cervical mucus methods, the symptothermal method, and the lactational amenorrhea method (LAM). *These fertility awareness–based (FAB) methods* use various techniques to determine a woman's fertile phase of the menstrual cycle, during which time intercourse should be avoided or another method of contraception used. Such techniques are typically chosen because they pose no health risks to the couple or to the fetus should pregnancy occur, or because of their lower cost or for religious reasons. In some cases, FAB methods are used by default because of a lack of access to or knowledge of other methods of contraception. Disadvantages of FAB methods include lack of STI protection, lower efficacy than for most other contraceptive methods, and the need for periods of abstinence or the use of another method of contraception, such as condoms, during fertile days.¹⁷

Calendar Methods

Calendar methods use a woman's monthly menstrual cycle length to calculate the fertile period. These methods factor in the viabilities of ovum (up to 24 hours) and sperm (3–5 days).¹⁸ Menstrual cycles may vary, so cycle lengths should be recorded for 6–12 cycles to predict the likely range of fertile days. The *calendar rhythm method* calculates the first fertile day in a woman's menstrual cycle by subtracting 18 from the number of days in her shortest cycle. The last fertile day is calculated by subtracting 11 from the number of days in her longest cycle. Women who have irregular cycles are not optimal candidates for this method, as an overestimation of unsafe fertile days could

occur.¹⁸ The *Standard Days Method* is a calendar method recommended only for women with cycles between 26 and 32 days in length. With the first day of menstruation counted as day 1, a woman should avoid intercourse on days 8–19 of her menstrual cycle or use another method of contraception, such as condoms, during this time.¹⁹

Cervical Mucus Methods

Cervical mucus methods rely on detection of changes in cervical secretions that take place during a normal menstrual cycle.¹⁹ Patients should be encouraged to work with trained instructors to ensure proper interpretation of mucus, as well as to avoid intercourse during the first cycle. Discussed next are two examples of such cervical mucus methods: the Billings Ovulation Method and the TwoDay Method.

With the *Billings Ovulation Method*, the woman observes the cervical mucus on a daily basis and charts its character and quantity. After menstruation, most women notice a sensation of vaginal dryness. Approximately 5–6 days before ovulation, estrogen levels rise, causing the cervical mucus to increase in quantity and elasticity and to become clear, resembling raw egg white. The peak symptom, correlated with the last day of detection of the clear, stretchy, estrogenic mucus, has been shown to occur within a day of ovulation for most women. With the postovulatory rise in progesterone, the mucus becomes thick and sticky or is absent. The woman is considered fertile from the first day after menstruation on which mucus is detected until 4 days after appearance of the peak symptom, during which time intercourse should be avoided.¹⁹ With experience and assistance, a woman learns to differentiate other vaginal secretions, such as seminal fluid after intercourse or an infectious discharge, from normal mucus, enabling her to seek early treatment for an infection. Patients should be informed that vaginal foams, gels, creams, and douches will interfere with cervical mucus.

Another method of monitoring cervical secretions is called the *TwoDay Method*.¹⁷ The woman should monitor for secretions on a daily basis, and if she notes any secretions that day or the day before, she is likely to be fertile. If she does not note any secretions, she is unlikely to be fertile. The TwoDay Method is a simple method that does not require keeping records or logs. However, patient education in identifying cervical secretions correctly is still important.¹⁸

Symptothermal Method

The symptothermal method combines cervical mucus tracking with basal body temperature (BBT) monitoring.¹⁹ Observation of the cervical mucus is used to identify the *onset* of the fertile period, whereas BBT charting is used to identify the *end* of the fertile period.¹⁶ Monitoring of BBT also can be used to predict ovulation for intended conception (see [Chapter 48](#)).

To monitor BBT, the woman charts her body temperature every morning, preferably with a digital thermometer calibrated in increments of 0.1°F (0.05°C), to detect small changes in body temperature.¹⁸ The temperature reading must be obtained at the same time every day, before getting out of bed, and is recorded on a chart or in an application for a smart phone ([Figure 10–2](#)). At least 3 hours of uninterrupted sleep are required for a reliable reading. The temperature may be taken orally, vaginally, or rectally, but the same site must be used each day.

Figure 10–2 Symptothermal variations during a model menstrual cycle.

(Source: Reprinted with permission from Jennings VH, Arevalo M, Kowal D. Fertility awareness–based methods. In: Hatcher RA, Trussell J, Stewart F, et al., eds. *Contraceptive Technology*. 18th rev ed. New York, NY: Ardent Media; 2004:327.)

In some women, the onset of ovulation may be detected by a drop in BBT 12–24 hours before ovulation. At the time of ovulation, BBT rises by at least 0.4°F (0.2°C) above the lowest point (the nadir).¹⁸ The postovulatory infertile time is typically identified once there have been at least 3–4 consecutive days of sustained elevated temperatures.¹⁸ Some women do not exhibit a definite or significant temperature dip or rise with ovulation. Stress, inadequate sleep, travel, fever, lactation, or perimenopause may affect BBT.¹⁸ For women who work rotating shifts, an accurate record of BBT may be difficult to maintain. At such times, couples should use an alternative method of contraception.

The Natural Cycles app for smartphones was approved by FDA in 2018 for use as a contraceptive strategy.⁴⁸ It is indicated for women 18 years and older who are premenopausal. For this method, daily BBT measurements are entered into the app, which also tracks the user's menstrual cycle. A proprietary

algorithm is employed to identify fertile and nonfertile days; the message “use protection” is displayed to signify the need for a contraceptive such as a condom or for abstinence during this period.⁴⁸ The app also can use data from urine luteinizing hormone (LH) test kits to improve the detection of ovulation, although this is not required for effectiveness. The Natural Cycles app is most appropriate for women with regular menstrual cycles, between 21 and 35 days in length, and is not meant for use with hormonal contraceptives or during breastfeeding, because ovulation is suppressed at that time.⁴⁸

Home Tests for Ovulation Prediction

Ovulation prediction tests are designed to aid couples in conceiving by detecting the surge in luteinizing hormone that occurs shortly before ovulation (see [Chapter 48](#)). These kits detect an increase in urinary excretion of the hormone, which usually occurs 8–40 hours before actual ovulation. These ovulation predictors do not give warning of impending ovulation with enough accuracy to be effective contraceptive agents and are not recommended for use other than as an aid for couples desiring pregnancy.¹⁸

Lactational Amenorrhea Method

In many developing countries, LAM is used as a contraceptive method for spacing the birth of children. When an infant younger than 6 months of age receives at least 90% of his or her nutrition from breastfeeding, and the mother is amenorrheic, LAM offers more than 98% protection against pregnancy.^{16,19} Because the suckling action of the infant on the breast at frequent intervals is necessary for LAM to be effective, milk extraction through a breast pump does not offer the same protection against pregnancy.¹⁹ Although menstrual periods in lactating women may be anovulatory, ovulation may occur before the return of menses. In general, if a breastfeeding woman is having menstrual periods, is supplementing her infant’s diet, or gave birth more than 6 months earlier, she should use an additional method of contraception.^{16,19} Among breastfeeding women whose infants receive almost all of their nutrition from breast milk, without supplementation, studies have reported pregnancy rates of 0.5%–2% for the 6-month period after giving birth. Once supplemental feedings begin, the efficacy rate decreases significantly.¹⁹

Effectiveness of Fertility Awareness–Based Methods

Overall, the pregnancy rate for typical use of FAB methods is approximately

15% (**Table 10–2**).¹⁷ In comparison with condoms, hormonal methods, or the nonhormonal IUC, the risk of pregnancy is higher with many of the FAB methods when used alone. Consequently, family planning professionals do not recommend relying on a single method; instead, they suggest using a combination of methods. FAB methods that specifically identify preovulatory and postovulatory changes, such as the symptothermal method, have better outcomes; with perfect use, the annual failure rate for the symptothermal method is less than 1%.¹⁷ The manufacturer information for the Natural Cycles app shows a “perfect use” failure rate of 1% and “typical use” failure rate of 7%–8%.^{17,48}

FAB methods also do not provide any protection against STIs and should be recommended solely for couples in mutually monogamous relationships.

Coitus Interruptus

For coitus interruptus (the withdrawal method), coital activity continues until ejaculation is imminent; then the penis is immediately withdrawn to allow ejaculation to occur away from the vagina or vulva. Method failures—that is, occurrence of pregnancy even when the method is used correctly and consistently—result in part because involuntary pre-ejaculation secretions may contain millions of sperm. Disadvantages of this method include the requirement for considerable self-control by the man, the potential for diminished pleasure for the couple related to interrupted lovemaking, and absence of STI protection. This method has failure rates of 4% with perfect use and 20% with typical use, comparable with those of barrier methods.⁴⁹

Algorithm: Unintended Pregnancy and STIs

Figure 10–1 Prevention of unintended pregnancy and sexually transmitted infections. Key: OTC = Over-the-counter; Rx = prescription; STI = sexually transmitted infection.

Assessment of Prevention of Pregnancy and

STIs: A Case-Based Approach

Before advising a couple on contraception and STI prevention, the health care provider must first identify their level of knowledge about these issues, because an understanding of their risk of pregnancy and STIs is essential to select an appropriate product or method. Persons who prefer FAB methods require basic knowledge of the reproductive cycle before they can use these methods effectively. Those who prefer nonprescription contraceptive products must know how to use them properly and be prepared to use them with every act of intercourse. The health care provider should identify individual preferences for products or methods on the basis of the timing of use or religious or cultural practices.

Case 10–1 illustrates the assessment of a man who is seeking advice on symptoms of a STI, whereas Case 10–2 deals with the use of EC.

Patient Counseling for Prevention of Pregnancy and STIs

Pharmacists are in a unique position to lower the incidence and consequences of unintended pregnancy and STIs in their communities. Many patient–provider interactions present opportunities for discussion of specific diseases or prevention strategies with persons who may be at high risk for unintended pregnancy and STIs. If possible, consultation involving both partners can improve their understanding and acceptance of selected contraceptive methods.

Health care providers must be familiar with the proper use of available nonprescription contraceptive products. Educational materials should be easily accessible by the patient, and opportunities for consultation should be maximized by removing potential barriers to open conversations (e.g., a noisy or overly structured physical environment that hinders personal encounters; a lack of personnel with second language skills as needed for effective provider–patient interactions). Pharmacists in some states may now provide hormonal contraception without a prescription, as summarized in the box “A Word About Provision of Hormonal Contraception by Pharmacists.”⁵⁰

In addition to an educational role, the health care provider may serve as a resource for access as needed to other medical and social supportive services. In cases of suspected domestic violence, child abuse, or sexual abuse, pharmacists often are designated mandatory reporters as specified by state law. Availability of a private area for education and counseling is important if adequate discussion is to take place.

Special efforts should be made to offer contraceptive information and services to adolescents. Health care providers who are uncomfortable discussing reproductive health in a nonjudgmental manner with young people should refer adolescents to a clinic that specializes in services for this age group. Adolescents need clear, accurate information on all aspects of reproductive health. An important consideration is that misconceptions about STIs and pregnancy risk as well as proper contraceptive use are common, especially among adolescents, so adequate education is very important. FAB methods are recommended for couples in a stable relationship. These methods, especially the symptothermal and cervical mucus methods, require extensive coaching and support from health care professionals who have experience with FAB methods. In addition to stocking spermicidal products, BBT thermometers, and monitoring charts, the pharmacist may serve as an educational resource for persons who want to use these methods of family planning. A pharmacist with the proper training might consider counseling patients on FAB methods as a unique practice possibility.

Case 10–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and	

Relevant Evaluation Criteria	Scenario/Model Outcome
medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient is asking for a recommendation for genital soreness and irritation. Patient states he has been experiencing some penile discharge and has had genital pain and irritation for 10 days. He states it started 2 days after having intercourse with his new girlfriend about 2 weeks ago. He states he thinks he has an allergy to the spermicide they were using instead of condoms. They recently had intercourse again, for which they did not use either a condom or the spermicide, but the discharge and pain are still present.
b. Patient's identity	Mark Stanton
c. Patient's age, gender, height, and weight	24 years, male, 5 ft 11 in., 160 lb
d. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	None; history of multiple sexual partners
e. Allergies	NKA
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Patient describes genital irritation with a discharge present. There is an increased risk for STI due to unprotected intercourse. An allergy to a spermicide does not usually result in a discharge, so a medical evaluation is needed. The patient also stated that they did not use spermicide again, but that he still has the irritation and discharge.

Relevant Evaluation Criteria	Scenario/Model Outcome
3. Identify exclusions for self-treatment.	The symptoms of genital discharge, pain, and irritation exclude the patient as a candidate for self-care. The symptoms could be caused by an STI, which will necessitate a primary care provider referral for testing and treatment.
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Recommend STI screening, evaluation, and treatment by a primary care provider. For future intercourse, recommend use of a male condom (Tables 10–4 through 10–6) with or without an additional spermicide to provide STI protection as well as contraception. The use of spermicide (Tables 10–8 and 10–9), however, has not been shown to improve protection against STIs. (2) Recommend STI screening, evaluation, and treatment by a primary care provider. For future intercourse, recommend use of a female condom (Table 10–7) to provide STI protection as well as contraception. (3) Recommend avoiding spermicidal products to see if irritation improves. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Mr. Stanton agrees to see his primary care provider to rule out an STI. He prefers to use a nonspermicidal male condom with additional spermicide to provide contraception and STI protection for future acts of sexual intercourse (if no allergy is determined).
6. Describe the recommended therapeutic	"Make an appointment to see your primary care provider as soon as possible to get testing for an STI. Your primary care provider will be able to determine the cause of your symptoms and treat you appropriately. If it is

Relevant Evaluation Criteria	Scenario/Model Outcome
approach to the patient or caregiver.	determined that you have an STI, inform all of your recent sexual partners so that they can be screened as well. For future prevention of an STI, use a nonspermicidal male condom plus additional spermicide (if it is determined that you do not have an allergy to spermicides) for each act of sexual intercourse.”
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	“Genital irritation and discharge, especially appearing after unprotected intercourse, could be signs of an STI. Discharge is not usually a symptom of irritation from a spermicide, so you need to get a proper evaluation. If testing shows you have an STI, you will need medical treatment. You also will need to let any sexual partners know about your STI so that they can be evaluated and treated if necessary. Delaying evaluation by a primary care provider could result in worsening of the infection and also may put your sexual partners at risk. Your health depends on awareness of the need to prevent STIs. Of the various OTC methods of contraception, such as condoms, sponges, and spermicide, only the male or female condom provides protection from STIs. So issues of STI prevention, in addition to contraception, are major considerations in beginning a sexual relationship.”
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
a. Appropriate dose and frequency of administration	“Use a fresh male condom and spermicide application (if it does not cause irritation for you or your partner) with each act of sexual intercourse.”
b. Product administration	See Tables 10–5 to 10–7 , and 10–9 .

Relevant Evaluation Criteria	Scenario/Model Outcome
procedures	
c. Expected time to onset of effect	"Once they are correctly placed, male condoms are effective immediately."
d. Degree of effectiveness that can be reasonably expected	See Table 10–2 for efficacy rates.
e. Most common adverse effects	"Irritation to the penis or vagina from exposure to latex or spermicide can occur. Some people have a sensitivity reaction to nonoxynol-9, the only spermicide currently available. The condom can also break or slip, allowing exposure to sperm and infection. Some men report reduced sensitivity and pleasure when using condoms."
f. Patient options in the event that condition worsens or persists	"Consult your primary care provider."
g. Product storage requirements	See Tables 10–5 and 10–7 .
Solicit follow-up questions from the patient or caregiver.	"Can I use lubricants with the condom?"
Answer the patient's or caregiver's questions.	"Yes, but the condom can be used with only certain lubricants that are water-based. Oil-based lubricants can damage the condom and should be avoided." (See Table 10–6 .)
Follow-up: Monitor and	

Relevant Evaluation Criteria	Scenario/Model Outcome
Evaluate	
9. Assess patient outcome.	Encourage Mr. Stanton to call the pharmacy if he has further questions.

Key: NKA = No known allergies; OTC = over-the-counter; STI = sexually transmitted infection.

Case 10–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient had unprotected intercourse with her spouse 2 days ago. She is concerned that she may become pregnant again, and she has a 10-week-old baby.

Relevant Evaluation Criteria	Scenario/Model Outcome
b. Patient's identity	Jenny Aronson
c. Patient's age, gender, height, and weight	27 years, female, 5 ft 2 in., 135 lb
d. Patient's occupation	College student
e. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	The patient gave birth 10 weeks ago. She is breastfeeding her infant and also using some formula supplementation.
	Occasional tension headaches: ibuprofen 200 mg 2 tablets orally every 8 hours as needed. Multivitamin 1 tablet daily; fluticasone (Flonase) nasal spray, 1 spray in each nostril daily as needed for seasonal allergies.
f. Allergies	Seasonal, NKDA
g. History of other adverse effects to medications	None
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Mrs. Aronson has an elevated risk of pregnancy due to unprotected intercourse.

Relevant Evaluation Criteria	Scenario/Model Outcome
3. Identify exclusions for self-treatment.	None. The patient's consultation is within therapeutic window of 120 hours after unprotected intercourse for OTC EC use.
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Recommend use of OTC levonorgestrel EC, because it is compatible with breastfeeding and she is within the window of 120 hours since unprotected intercourse occurred. Refer Mrs. Aronson to her primary care provider if her pregnancy test is positive. Recommend that she confirm her multivitamin has 400 mcg of folic acid to prevent neural tube defects in case she is pregnant. (2) Recommend against the use of OTC levonorgestrel EC, and refer Mrs. Aronson to her primary care provider for a prescription EC method and to discuss EC options while breastfeeding, such as ulipristal acetate or levonorgestrel. Recommend that Mrs. Aronson see her primary care provider if applicable for pregnancy testing and prenatal care. Also, if she is not pregnant, recommend that she seek a longer-term prescription contraceptive method, or recommend that she seek a self-administered hormonal contraceptive from a pharmacist if that is allowed in her state. Recommend that she confirm her multivitamin has 400 mcg of folic acid to prevent neural tube defects in case she is pregnant or becomes pregnant in the future. (3) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient	Mrs. Aronson prefers to purchase an OTC EC product at this time. Recommend that she see her primary care provider to have pregnancy screening and for prenatal care, if applicable.

Relevant Evaluation Criteria	Scenario/Model Outcome
preferences.	
6. Describe the recommended therapeutic approach to the patient or caregiver.	“You should use the nonprescription EC products because you are within the window of time that the product is effective in preventing pregnancy.” (See Table 10–10.)
	“If you are concerned about pregnancy, you could use the pregnancy test at home. Use the test first thing in the morning when you urinate. If the test is positive as indicated in the package information, see your primary care provider promptly. Keep in mind that home pregnancy tests may show false negatives early in the pregnancy, and seeing your primary care provider is the best way to determine whether you are pregnant. Your primary care provider also can provide prenatal care or a long-term contraceptive product if needed. Check your multivitamin to make sure it has 400 mcg of folic acid to help prevent neural tube defects in the event you are pregnant or become pregnant in the future.”
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	“Nonprescription EC is 52%–100% effective in preventing pregnancy and works best the sooner it is taken. The nonprescription EC product (levonorgestrel product) should be taken as soon as possible within 120 hours of unprotected intercourse and is compatible with breastfeeding. EC is most effective the sooner you take it after unprotected intercourse. Seeing your primary care provider for a prescription will delay time of administration and will may decrease effectiveness. In addition, a breastfeeding woman who takes ulipristal acetate must wait 24 hours after taking the product before resuming breastfeeding. It is not intended to be used during pregnancy. If you are pregnant, it is important to see your primary care provider for prenatal care to ensure the best outcome for you and your child. Continue to take your multivitamin, and check to see that it has 400 mcg of folic acid.”
Implement	
8. When recommending self-care with nonprescription medications and/or	(1) “The levonorgestrel EC product is given as a single dose and should be taken as soon as possible after unprotected intercourse. It is compatible with breastfeeding. It is not 100% effective but most effective when taken as soon as possible after unprotected intercourse. The method is effective when taken within 120 hours (per package labeling, within 72 hours).” (See Table 10–11 for EC counseling points.)(2) “Adverse effects of EC may include

Relevant Evaluation Criteria	Scenario/Model Outcome
nondrug therapy, convey accurate information to the patient or caregiver.	a change in menstrual cycle, depending on when the EC product is used. Patients may have their next menstrual period early or late or experience no change. If menstruation has not occurred more than 21 days after EC, you should take a pregnancy test.”(3) “EC is as effective as a regular contraceptive method. If you are sexually active and would like to prevent pregnancy, it is recommended that you begin using regular contraception after taking an EC product. Barrier methods should be used with each subsequent act of intercourse during the rest of the current menstrual cycle. Hormonal contraceptive methods may be started with the next menstrual period or may be started the day after taking the levonorgestrel EC product, with 7 days of a backup contraceptive method.”(4) “Check your multivitamin to make sure it has 400 mcg of folic acid to help prevent neural tube defects in the event you are pregnant.”
Solicit follow-up questions from the patient or caregiver.	(1) “Can I use EC as a regular birth control method?”(2) “What can I use over-the-counter to prevent pregnancy until I get a prescription contraceptive?”
Answer the patient’s or caregiver’s questions.	(1) “EC is not intended to be a regular form of birth control. For more effective and less expensive ways of contraception, you should see your primary care provider to obtain a prescription for a more regular form of contraception if you are not pregnant. Nonprescription contraceptives such as condoms, spermicides, and the sponge may also be an option.”(2) “Male or female condoms, a contraceptive sponge, or spermicides may be used to prevent pregnancy. Use a fresh condom (female or male) with each act of sexual intercourse. If using a spermicide, make sure to use a new spermicide application with each act of sexual intercourse.” (See Tables 10-5 to 10-7 and 10-9 for directions on using these various products.)
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Mrs. Aronson in a day or two to inquire if she has any questions regarding EC or needs assistance with obtaining a prescription for her usual contraceptive product.

Key: EC = Emergency contraception; NKDA = no known drug allergies; OTC = over-

the-counter; STI = sexually transmitted infection.

A Word About Provision of Hormonal Contraception by Pharmacists

Provision of hormonal contraception by a pharmacist has been shown to improve access to highly effective methods. This strategic health care approach is evolving and varies by state: Pharmacists in Washington have provided contraception through collaborative practice agreements for several decades. Oregon, California, Colorado, the District of Columbia, Hawaii, Maryland, Idaho, Utah, West Virginia, and New Mexico passed legislation allowing pharmacists to provide self-administered hormonal contraception without a prescription. Each state or district specifies which of the hormonal products, such as oral, transdermal, vaginal, and depot injectable, are available for pharmacist prescribing. As health care providers, pharmacists are involved in assessing women for potential medical contraindications to hormonal contraception before dispensing. Legislation to allow pharmacist contraceptive prescribing is being pursued in other states as well.

Evaluation of Patient Outcomes for Prevention of Pregnancy and STIs

Many sexually active persons are at risk for unintended pregnancy or STIs. The most important factor affecting the ability of a contraceptive to prevent pregnancy and STIs is correct and consistent use with each sexual encounter. Although any of the methods are effective for pregnancy prevention, use of male condoms (except for lamb cecum) or the female condom is the preferred

method for prevention of STIs. Patients who experience an adverse effect after use of a nonprescription contraceptive should switch to an alternative brand or agent. If the symptoms do not resolve or if they recur with the use of other agents, the affected person should seek medical attention. A sexually active woman who misses a menstrual period should be encouraged to perform a home pregnancy test or to seek medical attention. Symptoms of an STI in a sexually active person warrant medical referral ([Table 10-1](#)).

Key Points for Prevention of Pregnancy and STIs

- No method of contraception except abstinence is completely effective at preventing unintended pregnancy and STIs.
- The HPV vaccine is an effective method of preventing HPV infection–related consequences, including genital warts and cervical, vaginal, vulvar, penile, and anal cancers.
- Selection of a contraceptive product or method must be based on individual risk for undesired outcomes (pregnancy and STI) and efficacy, safety, and acceptability.
- Efficacy of nonprescription contraceptives is significantly increased by correct and consistent use of the product or method with each sexual encounter ([Tables 10-5](#) through 10-9).
- Male condoms (latex) and female condoms are the preferred contraceptive products for persons at recognized risk for STIs. Nonlatex condoms other than lamb cecum may be used in persons with latex hypersensitivity for STI prevention.
- Spermicides decrease risk of unintended pregnancy but may increase risk of STIs.
- Vaginal spermicides are available in different dosages and forms to improve patient acceptability.
- EC is an effective method of postcoital contraception that can

decrease the risk of unintended pregnancy, but not the risk of STIs. EC should not be used as routine contraception.

- FAB methods constitute an inexpensive, modestly effective approach to contraception that can be used by couples in a mutually monogamous relationship.

Chapter 11: Colds and Allergy

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Colds

A *cold*, also known as the common cold, is a viral infection of the upper respiratory tract. According to some estimates, 1 billion cases of the common cold occur annually, making it one of the top five illnesses diagnosed in the United States.^{1,2} Adults usually have 2–3 colds per year, whereas children may experience 6 or more.² Colds may occur at any time of the year, but the incidence tends to be higher in winter months.²

Colds constitute the leading cause of work and school absenteeism. A cold is usually a self-limiting illness; however, because symptoms are bothersome, patients frequently self-medicate, with an estimated \$8 billion spent annually on nonprescription cold and cough products.³

Pathophysiology of Colds

More than 200 viruses are recognized to cause colds. A majority of colds in children and adults are due to rhinoviruses.^{1,2} Other viruses known to cause colds include coronaviruses, parainfluenza, respiratory syncytial virus, adenoviruses, and human metapneumovirus. Coinfection with bacteria (usually group A beta-hemolytic streptococci) occurs but is rare. Rhinoviruses are RNA viruses, with more than 100 serotypes. The viral infection is limited to the upper respiratory tract and primarily affects the following respiratory structures: pharynx, nasopharynx, nose, cavernous sinusoids, and paranasal sinuses. The respiratory tract's intricate host defense system usually protects the body from infectious and foreign particles. The respiratory tract, especially the nose, is well perfused by blood vessels and well innervated. The nose contains sensory, cholinergic, and sympathetic nerves. When stimulated by an infectious (e.g., a cold) or allergic (e.g., allergic rhinitis) process, those nerves play a role in the resulting symptoms and also serve as targets for some nonprescription therapies. Stimulation of sensory fibers by mechanical and thermal stimuli or by mediators such as histamine and bradykinin results in

sneezing. Cholinergic and sympathetic nerves are involved in congestion in that they innervate glands and arteries that supply the glands. Cholinergic stimulation dilates arterial blood flow, whereas sympathetic stimulation constricts arterial blood flow. The sensory, cholinergic, and sympathetic nerves also respond to a variety of neuropeptide neurotransmitters.

A cold develops after a rhinovirus (or similar virus) binds to intercellular adhesion molecule-1 receptors on respiratory epithelial cells in the nose and nasopharynx.⁴ Once inside the epithelial cells, the virus replicates, and infection spreads to other cells.⁴ Peak viral concentrations are achieved 2–4 days after initial inoculation, and viruses are present in the nasopharynx for 16–18 days.⁴ Infected cells release chemokine “distress signals,” and cytokines then activate inflammatory mediators and neurogenic reflexes. These activation processes result in recruitment of additional inflammatory mediators, vasodilation, transudation of plasma, glandular secretion, and stimulation of pain nerve fibers and sneeze and cough reflexes. Inflammatory mediators and parasympathetic nervous system reflex mechanisms cause hypersecretion of watery nasal fluid. Viral infection ends once enough neutralizing antibody (secretory immunoglobulin A [IgA] or serum IgG) leaks into the mucosa to end viral replication.

The most efficient mode of viral transmission is self-inoculation of the nasal mucosa or conjunctiva after contact with virus-laden secretions, typically present on the hands but also found on inanimate objects (e.g., doorknobs, telephones). Transmission by means of inhalation of aerosolized viral particles also is common. Increased susceptibility to colds has been linked to higher exposure rates (e.g., with increased population density in classrooms or day care centers); allergic disorders affecting the nose or pharynx; less diversity in today’s social networks, with restricted exposure to pathogens; and a weakened immune system secondary to smoking, a sedentary lifestyle, chronic (i.e., ≥ 1 month) psychological stress, or sleep deprivation (e.g., poor sleep quality or < 7 hours of sleep per night).^{2,5,6} Conflicting information has emerged about increased susceptibility related to cold environments, sudden chilling, or exposure to central heating (i.e., low humidity).⁷ Stressors such as walking outside barefoot, teething, and suffering from enlarged tonsils or adenoids have not been shown to increase susceptibility to viral upper respiratory infections.²

Clinical Presentation of Colds

A predictable sequence of clinical manifestations begins 1–3 days after infection.⁴ Sore throat is the first symptom to emerge, followed by nasal symptoms, which dominate 2–3 days later. Cough develops in 30% of patients by day 4 or 5. Physical assessment may yield the following findings: slightly red pharynx with evidence of postnasal drip, nasal obstruction, and mild to moderate tenderness to palpation of sinuses. During the first 2 days of a cold, the patient may report clear, thin, and/or watery nasal secretions. As the cold progresses, the secretions become thicker and the color may change to yellow or green with the influx of polymorphonuclear cells. This change does not indicate bacterial infection. When the cold begins to resolve, the secretions again become clear, thin, and/or watery. Low-grade fever may be present, especially in children, but colds are rarely associated with an oral temperature above 100.4°F (38°C) or rectal or tympanic temperature above 100.9°F (38.3°C). Rhinovirus cold symptoms persist for approximately 7–14 days.⁴ Signs and symptoms of a cold may be confused with those of influenza and other respiratory illnesses ([Table 11–1](#)).

Table 11–1 Differentiating Characteristics of Colds and Other Respiratory Disorders	
Illness	Signs and Symptoms
Allergic rhinitis	Watery eyes; itchy nose, eyes, or throat; repetitive sneezing; nasal congestion; watery rhinorrhea; red, irritated eyes with conjunctival injection
Asthma	Cough, dyspnea, wheezing
Bacterial throat infection	Sore throat (moderate–severe pain), fever, exudate, tender anterior cervical adenopathy
Colds	Sore throat (mild–moderate pain), nasal congestion, rhinorrhea, sneezing common; low-grade fever, chills, headache, malaise, myalgia, and cough possible
Croup	Fever, rhinitis, and pharyngitis initially, progressing to cough (may be “barking” cough), stridor, and dyspnea
Influenza	Myalgia, arthralgia, fever with oral T ≥100.4°F–102°F (38°C–38.9°C), sore throat, nonproductive cough, moderate–severe fatigue
Otitis	Ear popping, ear fullness, otalgia, otorrhea, hearing loss, dizziness

Illness	Signs and Symptoms
media	
Pneumonia or bronchitis	Chest tightness, wheezing, dyspnea, productive cough, changes in sputum color, persistent fever
Sinusitis	Tenderness over the sinuses, facial pain aggravated by Valsalva maneuver or postural changes, fever with oral T >101.5°F (38.6°C), tooth pain, halitosis, upper respiratory tract symptoms for >7 days with poor response to decongestants
West Nile virus infection	Fever, headache, fatigue, rash, swollen lymph glands, and eye pain initially, possibly progressing to gastrointestinal distress, central nervous system changes, seizures, or paralysis
Whooping cough	Initial catarrhal phase (rhinorrhea, mild cough, sneezing) of 1–2 weeks, followed by 1–6 weeks of paroxysmal coughing

Key: T = Temperature.

Most people do not experience complications from colds. However, such complications may be severe and, rarely, life-threatening. Disorders potentially resulting from colds include sinusitis, middle ear infections, bronchitis, pneumonia, and exacerbations of asthma or chronic obstructive pulmonary disease.

Treatment of Colds

Treatment Goals

Because there is no known cure for colds, the goal of therapy is to reduce bothersome symptoms while preventing transmission of cold viruses to other persons.

General Treatment Approach

Antibiotics are ineffective against viral infections, and the mainstay of

treatment is nonpharmacologic therapy. If the patient desires to self-treat, a stepwise approach using single-entity products targeting specific symptoms is preferred over the use of combination products (Figure 11-1), because symptoms appear, peak, and resolve at different times.⁴ Patient education regarding the administration of intranasal drugs (Table 11-2) and ophthalmic preparations (see Chapter 28) is an important component of management. Not all patients should self-treat for a cold (see the exclusions for self-treatment listed in Figure 11-1).

Table 11-2 Administration Guidelines for Nasal Dosage Formulations	
General Instructions • Clear nasal passages before administering the product. • Wash your hands before and after use. • Gently depress the other side of the nose with finger to close off the nostril not receiving the medication. • Aim tip of delivery device away from nasal septum to avoid accidental damage to the septum. • Breathe through mouth and wait a few minutes after using the medication before blowing the nose.	
Nasal Sprays • Gently insert the bottle tip into one nostril, as shown in drawing A. • Keep head upright. Sniff deeply while squeezing the bottle. Repeat with other nostril.	Nasal Inhalers • Warm the inhaler in hand just before use. • Gently insert the inhaler tip into one nostril, as shown in drawing B, while inhaling. • Wipe the inhaler after each use. Discard after 2-3 months if it smells medicinal.



A



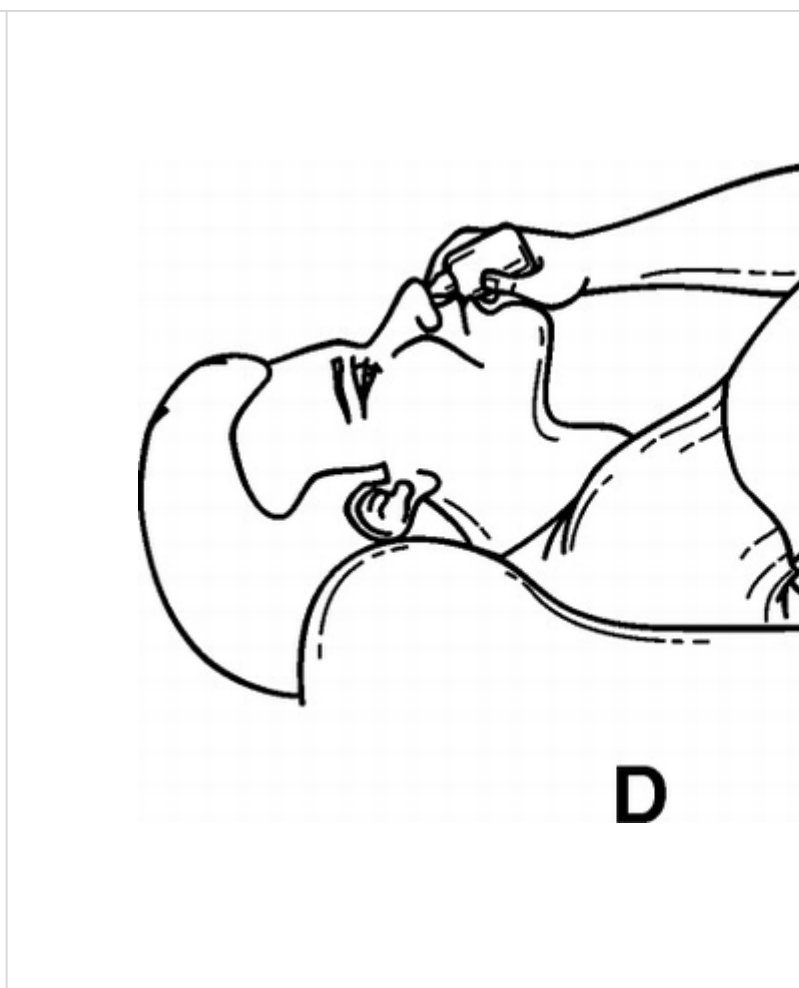
C

Pump Nasal Sprays

- Prime the pump before using it the first time. Hold the bottle with the nozzle placed between the first two fingers and the thumb placed on the bottom of the bottle.
- Tilt the head forward.
- Gently insert the nozzle tip into one nostril, as shown in drawing B. Sniff deeply while depressing the pump once.
- Repeat with other nostril.

Nasal Drops

- Lie on bed with head tilted back and over the side of the head.
- Squeeze the bulb to withdraw medication from the bottle.
- Place the recommended number of drops into one nostril.
- Repeat with other nostril. Lie on bed for 1-2 minutes after use.
- Do not rinse the dropper.



Note: Do not share the drug or its dispenser with anyone. Discard solutions if discolored or if contamination is suspected. Remove caps before use and replace tightly after each use. Do not use expired products.

Table 11-3 Dosage Guidelines for Nonprescription Systemic Nasal Decongestants

Drug	Dosage ^a (maximum daily dosage)		
	Adults and Children ≥ 12 Years	Children 6 to < 12 Years	Children 2 to < 6 Years ^b
Phenylephrine HCl	10 mg every 4 hours (60 mg)	5 mg every 4 hours (30 mg)	2.5 mg every 4 hours (15 mg)
Phenylephrine bitartrate	15.6 mg every 4 hours (62.4 mg)	7.8 mg every 4 hours (31.2 mg)	Not recommended for children <6 years except under advice of HCP

Drug	Dosage ^a (maximum daily dosage)		
	Adults and Children ≥ 12 Years	Children 6 to < 12 Years	Children 2 to < 6 Years ^b
Pseudoephedrine	60 mg every 4–6 hours (240 mg)	30 mg every 4–6 hours (120 mg)	15 mg every 4–6 hours (60 mg)

^a Taken as needed.

^b FDA has advised that cough and cold medications not be used in children younger than 2 years of age.¹² Manufacturers have voluntarily updated cough and cold product labels to state “do not use” in children younger than 4 years of age.¹³

Key: FDA = U.S. Food and Drug Administration; HCP = health care provider.

Source: [Reference 11](#).

Table 11–4 Dosage Guidelines for Nonprescription Topical Nasal Decongestants

Drug	Concentration (%)	Adults and Children ≥12 Years	Children 6 to < 12 Years	Children 2 to < 6 Years ^a
Sprays/Drops				
Ephedrine ^b	0.5	2–3 drops/sprays in each nostril not more often than every 4 hours	1–2 drops/sprays in each nostril not more often than every 4 hours	Not recommended for children <6 years except under advice of HCP
Levmetamfetamine	0.04–0.15 mg/800 mL of air	2 inhalations in each nostril not more often than every 2 hours	1 inhalation in each nostril not more often than every 2 hours	Not recommended for children <6 years except under advice of HCP
Naphazoline	0.05	1–2 drops/sprays in each nostril not more often than every	Not recommended for children <12 years except	Not recommended for children <6 years except

Drug	Concentration (%)	Adults and Children ≥12 Years	Children 6 to < 12 Years	Children 2 to < 6 Years^a
Sprays/Drops				
		6 hours	under advice of HCP	under advice of HCP
	0.025	–	1–2 drops/sprays in each nostril not more often than every 6 hours	Not recommended for children <6 years except under advice of HCP
Oxymetazoline	0.05	2–3 drops/sprays in each nostril not more often than every 10–12 hours (maximum: 2 doses/ 24 hours)	2–3 drops/sprays in each nostril not more often than every 10–12 hours (maximum: 2 doses/ 24 hours)	Not recommended for children <6 years except under advice of HCP
	0.025	–	–	2–3 drops/sprays in each nostril not more often than every 10–12 hours (maximum: 2 doses/ 24 hours)
Phenylephrine	1.0	2–3 drops/sprays in each nostril not more often than every 4 hours	Not recommended for children <12 years except under advice of HCP	Not recommended for children <6 years except under advice of HCP
	0.5	2–3 drops/sprays in each nostril not more often than every 4 hours	Not recommended for children <12 years except under advice of HCP	Not recommended for children <6 years except under advice of HCP
	0.25	2–3 drops/sprays in each	2–3 drops/sprays in each	Not recommended

Drug	Concentration (%)	Adults and Children ≥12 Years	Children 6 to < 12 Years	Children 2 to < 6 Years^a
Sprays/Drops				
		nostril not more often than every 4 hours	nostril not more often than every 4 hours	for children <6 years except under advice of HCP
	0.125	–	–	2–3 drops/sprays in each nostril not more often than every 4 hours
Propylhexedrine	0.4–0.5 mg/800 mL of air	2 inhalations in each nostril not more often than every 2 hours	2 inhalations in each nostril not more often than every 2 hours	Not recommended for children <6 years except under advice of HCP
Xylometazoline ^b	0.1	2–3 drops/sprays in each nostril not more often than every 8–10 hours	Not recommended for children <12 years except under advice of HCP	Not recommended for children <6 years except under advice of HCP
	0.05	–	2–3 drops/sprays in each nostril not more often than every 8–10 hours	2–3 drops/sprays in each nostril not more often than every 8–10 hours (maximum: 3 doses/ 24 hours)

^a No recommended dosages exist for children younger than 2 years of age, except under the advice and supervision of an HCP.

^b Products approved by FDA but nasal formulations are not currently marketed in the United States. Epinephrine is available as an oral inhaler (Primatene Mist, 0.125 mg/spray). See “Allergic Rhinitis” section for more information.

Key: FDA = U.S. Food and Drug Administration; HCP = health care provider.

Source: [Reference 11](#).

Nonpharmacologic Therapy

Although evidence of efficacy is lacking, popular therapeutic measures include increased fluid intake, adequate rest, a nutritious diet as tolerated, and increased humidification with steamy showers, vaporizers, or humidifiers. Vaporizers superheat water to produce steam and can deliver medications such as Vicks VapoSteam (camphor 6.2%). By contrast, humidifiers use fans or ultrasonic technology to produce a cool mist and cannot accommodate liquid additives. Saline nasal sprays or drops moisten irritated mucosal membranes and loosen encrusted mucus; salt gargles may ease sore throats. Hot tea with lemon and honey, chicken soup, and vegetable and other broths are soothing. Limited evidence suggests that a number of substances in chicken soup could have anti-inflammatory activity.⁸ Milk products should not be withheld, in view of the lack of evidence that milk increases cough or congestion. Medical devices such as Breathe Right nasal strips are marketed for temporary relief from nasal congestion and stuffiness resulting from colds and allergies. Those devices lift the nares open, thereby enlarging the anterior nasal passages. Aromatic oils (e.g., camphor, menthol, eucalyptus) contained in products such as Vicks VapoRub (for patients 2 years of age and older) ease nasal congestion and improve sleep by producing a soothing sensation.⁹ Children should be supervised closely when these products are used because aromatic oils can irritate the eyes and skin, and extensive exposure through inhalation or accidental ingestion can lead to toxicity.

Nondrug therapy for all patients, especially for infants, includes upright positioning to enhance nasal drainage. Because children typically cannot blow their own noses until the age of approximately 4 years, carefully clearing the nasal passageways with a nasal aspirator (e.g., bulb syringe, NoseFrida) may be necessary if accumulation of mucus interferes with sleeping or eating. Nasal aspirators may be mechanically or manually operated. To use a bulb syringe and avoid harm to the child, the caregiver should squeeze the large end of the bulb *before* inserting it, continue this compression while gently inserting the tip into the infant's nose, and then slowly release the squeezing pressure to

draw out fluid. After the pressure is completely released, the syringe is removed from the infant's nose and the fluid expelled from the syringe by again compressing the bulb. By contrast, NoseFrida is placed against the child's nostril, creating a seal, and the caregiver uses oral suction to remove mucus.

Proper hand hygiene reduces the transmission of cold viruses. The Centers for Disease Control and Prevention (CDC) encourages frequent hand cleansing with soap or soap substitutes such as hand sanitizers.² Not all hand sanitizers are effective at eradicating rhinoviruses from the skin. In a review of the safety and effectiveness of consumer and health care antiseptics, FDA determined that only three ingredients were eligible to be marketed in consumer antiseptic rubs: benzalkonium chloride; alcohol (ethyl alcohol or ethanol, 60%–95%); and isopropyl alcohol (70%–91.3%).¹⁰ The agency also determined that 28 ingredients, including chlorhexidine gluconate, iodine complex, and triclosan, were ineligible. Alcohol-based nasal sanitizers (e.g., Nozin) are available, but evidence of their efficacy against cold viruses is lacking. Use of antiviral disinfectants such as Lysol (which kills <99% of rhinoviruses after contact for 1 minute) and antiviral tissues such as Kleenex Anti-Viral (incorporating a tissue layer containing citric acid and sodium lauryl sulfate) also may help prevent transmission of viruses.

Pharmacologic Therapy

Decongestants

Decongestants specifically treat sinus and nasal congestion. Decongestants are adrenergic agonists (sympathomimetics). Stimulation of alpha-adrenergic receptors constricts blood vessels, thereby decreasing sinusoid vessel engorgement and mucosal edema. Three types of decongestants are available. *Direct-acting* decongestants (e.g., phenylephrine, oxymetazoline, tetrahydrozoline) bind directly to adrenergic receptors. *Indirect-acting* decongestants (e.g., ephedrine) displace norepinephrine from storage vesicles in prejunctional nerve terminals, and tachyphylaxis can develop as stored neurotransmitter is depleted. *Mixed* decongestants (e.g., pseudoephedrine) have both direct and indirect activity.

Systemic nonprescription decongestants include pseudoephedrine and phenylephrine. Intranasal nonprescription decongestants include the short-

acting decongestants ephedrine, levmetamfetamine (L-desoxyephedrine), naphazoline, phenylephrine, and propylhexedrine, and the long-acting decongestants xylometazoline (8–10 hours) and oxymetazoline (12 hours). Ophthalmic nonprescription decongestants also are available (see [Chapter 28](#)).

Systemic decongestants are rapidly metabolized by monoamine oxidase (MAO) and catechol-O-methyltransferase in the gastrointestinal (GI) mucosa, liver, and other tissues. Pseudoephedrine is well absorbed after oral administration; phenylephrine has a low oral bioavailability (approximately 38%). Both pseudoephedrine and phenylephrine have short half-lives (pseudoephedrine: 6 hours; phenylephrine: 2.5 hours), and peak concentrations for both drugs are reached at 0.5–2 hours after oral administration.

Decongestants are indicated for temporary relief of nasal and eustachian tube congestion and for cough associated with postnasal drip. Nonprescription decongestants are not approved by the U.S. Food and Drug Administration (FDA) to self-treat nasal congestion associated with sinusitis.

FDA-approved dosages for decongestants are listed in Tables [11–3](#)^{11,12} and [11–4](#).¹¹ (Note: In 2008, manufacturers voluntarily updated cough and cold products labels to state “do not use” in children under 4 years of age.¹³) Nonprescription decongestants are marketed in a variety of dosage formulations, and many combination products are available ([Table 11–5](#)).

Table 11–5 Selected Nonprescription Products for Nasal Decongestion	
Trade Name	Primary Ingredient(s)
Topical Decongestants	
Afrin Original Nasal Spray	Oxymetazoline HCl 0.05%
Vicks Sinex Nasal Spray	Oxymetazoline HCl 0.05%
4-Way Fast Acting	Phenylephrine HCl 1%
Neo-Synephrine Mild Strength Nasal Spray	Phenylephrine HCl 0.25%
Little Remedies Decongestant Nose Drops	Phenylephrine HCl 0.125%
Otrivin Medicated Cold &	Xylometazoline 0.1%

Trade Name	Primary Ingredient(s)
Allergy Relief (Canada)	
Nasal Decongestant Inhalers	
Benzedrex Inhaler	Propylhexedrine 250 mg
Vapor Inhaler	Levmetamfetamine (l-desoxyephedrine) 50 mg/inhaler
Systemic Decongestants	
Sudafed PE Congestion	Phenylephrine HCl 10 mg
Sudafed 24 Hour	Pseudoephedrine HCl 240 mg
Sudafed 12 Hour	Pseudoephedrine HCl 120 mg
Nexafed ^a	Pseudoephedrine HCl 30 mg
Zephrex-D ^b	Pseudoephedrine HCl 30 mg
Combination Products	
Sudafed PE Pressure + Pain	Phenylephrine HCl 5 mg; acetaminophen 325 mg
Alka-Seltzer Plus Cold	Phenylephrine bitartrate 7.8 mg; aspirin 325 mg; chlorpheniramine maleate 2 mg
Vicks Dayquil Cold & Flu Relief Liquicaps	Phenylephrine HCl 5 mg; acetaminophen 325 mg; dextromethorphan hydrobromide 10 mg
Tylenol Cold Max Nighttime Cool Burst Liquid ^c	Phenylephrine HCl 5 mg/15 mL; acetaminophen 325 mg/15 mL; dextromethorphan hydrobromide 10 mg/15 mL; doxylamine succinate 6.25 mg/15 mL
Mucinex Children's Stuffy Nose & Chest Congestion Liquid	Phenylephrine HCl 2.5 mg/5 mL; guaifenesin 100 mg/5 mL
Aleve-D Sinus & Cold	Pseudoephedrine HCl 120 mg; naproxen sodium 220 mg
Mucinex D	Pseudoephedrine HCl 60 mg; guaifenesin 600 mg
Other Products	

Trade Name	Primary Ingredient(s)
Ocean Premium Saline Nasal Spray	Sodium chloride 0.65%
Vicks VapoRub	Camphor (4.8%); eucalyptus (1.2%); menthol (2.6%)

^a “Meth-detering” technology (Impede) (i.e., drug is designed to deter the conversion of pseudoephedrine to methamphetamine).

^b “Meth-detering” technology (Tarex).

^c Contains 0.5% alcohol.

Adhering to FDA-approved doses of decongestant products is very important in that acute overdose can be life-threatening, especially in children. Systemic decongestant overdoses cause excessive central nervous system (CNS) stimulation, paradoxical CNS depression, cardiovascular collapse, shock, and coma. Treatment for decongestant overdoses is supportive.

Adverse effects associated with decongestants include cardiovascular stimulation (leading to elevated blood pressure, tachycardia, palpitations, or arrhythmias) and CNS stimulation (causing restlessness, insomnia, anxiety, tremors, fear, or hallucinations). Children and older adults are more likely than persons in other age groups to experience adverse effects. Adverse effects are more common with systemic decongestants, because topical decongestants are minimally absorbed. However, accidental ingestion of nasal or ophthalmic decongestants can cause adverse effects ranging from nausea, vomiting, and drooling to more serious derangements including hypotension, hyperthermia, lethargy, sedation, and coma. Adverse effects specifically related to topical decongestants include propellant- or vehicle-associated effects (e.g., burning, stinging, sneezing, local dryness) and trauma from the tip of the administration device. Rhinitis medicamentosa (RM)—that is, rebound congestion—has been associated with use of topical decongestants. The exact cause is unknown, but short-acting products, preservative agents (e.g., benzalkonium chloride), and long duration of therapy are suspected as contributing factors.¹⁴ Depending on the active ingredient, limiting therapy to 3–7 days is the accepted approach to avoid RM. However, controversy exists,

and some studies show that treatment duration of 10 days to 8 weeks appears to be safe and does not cause RM.¹⁴ Further investigation is needed to determine the optimal duration of treatment. Treatment for RM consists of slowly withdrawing the topical decongestant (restricted to one nostril at a time); replacing the decongestant with topical normal saline, which soothes the irritated nasal mucosa; and, if needed, using topical corticosteroids and systemic decongestants. A withdrawal period of 2–6 weeks of such measures may be needed before mucous membranes return to normal. A nonprescription kit, RhinoStat, has been advertised to assist health care providers and patients with management for RM. The product creates a patient-specific mixture of the implicated topical decongestant product and a diluent; of note, however, the kit is not FDA approved.

Decongestants interact with numerous drugs, as summarized in [Table 11–6](#). Decongestants are contraindicated in patients receiving concomitant MAO inhibitors (MAOIs).

Table 11–6 Clinically Important Drug–Drug Interactions With Cold and Allergy Products

Drug/Drug Class	Potential Interaction (with drug-specific data)	Management/Prevention
Decongestants		
Ergot derivatives (e.g., dihydroergotamine and ergotamine)	Increased risk of hypertension and vasoconstriction	Avoid combination.
Linezolid	Increased risk of hypertension	Reduce dose of decongestant and monitor closely. Consider therapy modification.
MAOIs (e.g., phenelzine, selegiline)	Increased risk of hypertension	Avoid combination.
Serotonin/norepinephrine reuptake inhibitors	Increased risk of tachycardia	Consider therapy modification.
Antihistamines		
Amiodarone	Increased risk of QT interval prolongation (loratadine)	Avoid combination.

Drug/Drug Class	Potential Interaction (with drug-specific data)	Management/Prevention
Antacids (aluminum and magnesium salts)	Decreased efficacy (fexofenadine)	Separate doses by as much time as possible.
Anticholinergics (e.g., ipratropium, tiotropium, umecclidinium)	Enhanced anticholinergic effects (dry mouth, eyes, urinary retention, sedation)	Avoid combination.
Brexpiprazole	Increased risk of brexpiprazole toxicity (diphenhydramine)	Reduce brexpiprazole dose by 25% or avoid combination.
CNS depressants (alcohol, opiates, sedatives)	Increased sedation (sedating antihistamines; cetirizine, levocetirizine)	Avoid combination.
Erythromycin; ketoconazole	Increased fexofenadine plasma concentration	Monitor therapy closely.
Metoprolol	Increased metoprolol serum concentrations and risk of hypotension (diphenhydramine)	Reduce metoprolol dose or avoid combination.
Phenytoin	Decreased phenytoin elimination (chlorpheniramine)	Monitor therapy or avoid combination.
Potassium chloride (oral)	Increased risk of ulcers	Avoid combination.
Intranasal Corticosteroids		
Protease inhibitors (e.g., ritonavir, tipranavir, telaprevir)	Increased serum concentration of steroids (budesonide, fluticasone)	Avoid combination.

Key: CNS = Central nervous system; MAOI = monoamine oxidase inhibitor.

Source: Lexi-Comp Online. Hudson, OH: Wolters Kluwer. Available at: <https://online.lexi.com/lco/action/login>. (Subscription required.) Accessed June 7, 2019.

Decongestants may exacerbate diseases and conditions associated with sensitivity to adrenergic stimulation, such as hypertension, coronary heart

disease, ischemic heart disease, diabetes mellitus, hyperthyroidism, elevated intraocular pressure, and prostatic hypertrophy. Patients with hypertension should use decongestants only with medical advice, and no clear evidence has emerged to show that any one agent is safest in this population. Products specifically marketed for patients with hypertension (e.g., Coricidin HBP) do not contain decongestants. Those products usually consist of a combination of ingredients that may or may not be appropriate, depending on the patient's symptoms.

Health care providers should be aware of the possibility that purchase of large quantities of pseudoephedrine may be specifically for illegal use to produce methamphetamine. In 2005, passage of the Combat Methamphetamine Epidemic Act changed the classification of pseudoephedrine to "scheduled listed chemical products."¹⁵ That change in classification allowed limits to be placed on pseudoephedrine sales. All pseudoephedrine products must now be kept in secure areas (e.g., behind a pharmacy counter or in a locked cabinet), and purchases are limited to 3.6 g daily and 9 g per month per patient.¹⁵ The following information from each sale must be entered into a paper or electronic logbook: product name, quantity sold, patient's name and address, and time and date of sale.¹⁵ Patients must show valid identification to purchase pseudoephedrine and then sign the logbook. Some states and corporations have enacted stricter guidelines regarding the sale of pseudoephedrine.

Antihistamines

Monotherapy with nonprescription antihistamines may provide some benefit in adults if started early in the course of a cold (i.e., day 1 or 2 of symptom onset).¹⁶ Also, a combination of first-generation (sedating) antihistamines and decongestants showed some benefit in adults, but the significance of the data is questionable.¹⁷ Apart from questions of efficacy, an important issue is whether potential benefits of sedating antihistamines outweigh known risks associated with these drugs. (See later discussion of antihistamines for the topic "Allergic Rhinitis.")

Local Anesthetics

A variety of products containing local anesthetics (e.g., benzocaine, dyclonine hydrochloride) are available for the temporary relief of sore throats ([Table 11-7](#)).

Local anesthetic products may be used every 2–4 hours. Patients with a history of allergic reactions to anesthetics should be advised to avoid products containing benzocaine. Benzocaine also has been associated with methemoglobinemia, especially in children younger than 2 years, and should be avoided in this age group. Some products contain local antiseptics (e.g., cetylpyridinium chloride, hexylresorcinol) and/or menthol or camphor. Local antiseptics are not effective for viral infections. Emerging evidence suggests that menthol and camphor provide pain relief by stimulation of the TRPM8 or “menthol” receptor.¹⁸

Table 11-7 Selected Nonprescription Products for Sore Throat	
Trade Name	Primary Ingredient(s)
Lozenges	
Cepacol Sore Throat Extra Strength	Benzocaine 15 mg; menthol 3.6 mg
Chloraseptic Sore Throat	Benzocaine 6 mg; menthol 10 mg
Halls Fruit Breezers	Pectin 7 mg
Sucrets Sore Throat	Dyclonine HCl 2 mg
Vicks VapoDrops	Menthol 1.7 mg (cherry)
	Menthol 3.3 mg (menthol)
Throat Sprays	
Chloraseptic Sore Throat	Phenol 1.4%

Systemic Analgesics

Systemic analgesics (e.g., aspirin, acetaminophen, ibuprofen, naproxen) are effective for aches or fever sometimes associated with colds. Concerns that use of aspirin and acetaminophen may increase viral shedding and prolong illness have not been validated.¹⁹ Because of the risk of Reye syndrome, aspirin and aspirin-containing products should not be used in children or teenagers who have or are recovering from chickenpox or influenza-like symptoms. (See [Chapter 5](#) for a complete discussion of those products, including the manufacturer’s voluntary reduction of maximum daily dosages of Tylenol products sold in the United States [see under “Acetaminophen” and Table 5–3],

and developments in liquid infant acetaminophen products [see under “Patient Factors”].)

Antitussives and Protussives (Expectorants)

When present, cough associated with colds usually is nonproductive. Antitussive agents (codeine and dextromethorphan) are of questionable efficacy in colds, and their use in this setting is not recommended.²⁰ Guaifenesin, an expectorant, has not been proved effective in natural colds.²⁰ (See [Chapter 12](#) for a complete discussion of these products.)

Combination Products

Decongestants and antihistamines are marketed in many combinations, including combinations with analgesics, expectorants, and antitussives. Products also are marketed for daytime or nighttime use. Products for nighttime use usually contain a sedating antihistamine, whereas daytime products do not; rather they contain systemic decongestants to promote wakefulness. Combination products are convenient, but this benefit must be weighed against the risks associated with taking unnecessary drugs.

Pharmacotherapeutic Comparison

As stated earlier, evidence does not support the use of antitussives and expectorants and is limited for the use of antihistamines to treat symptoms related to colds. The use of local anesthetics and systemic analgesics for treatment of pain related to sore throat or of fever related to colds, however, is supported by good evidence.

Topical decongestants are convenient dosage forms and are effective in relieving nasal congestion; however, duration of their use is limited to 3–7 days owing to concerns about development of RM. The major differences between topical decongestants are in duration of action, dosage formulation (e.g., mist versus spray versus drops), moisture content, and preservative content.

Although many manufacturers have reformulated products with phenylephrine as a response to pseudoephedrine regulations, controversy remains with regard to the relative safety and efficacy of the systemic decongestants.^{21,22} Efficacy of the current FDA-approved dose of

phenylephrine has been extensively debated, and a citizen's petition was filed in 2015 to remove it from the nonprescription drug market.^{21,22}

Product Selection Guidelines

Special Populations

Drug use during pregnancy and lactation requires a balance between risk and benefit. (See the Preface for a detailed explanation of the pregnancy data.) Because most colds are self-limiting, with bothersome rather than life-threatening symptoms, many health care providers recommend nondrug therapy. When drugs are considered, agents with a long record of safety in animals and humans are preferred. To minimize possible adverse effects on the fetus or newborn, pharmacists should advise pregnant or lactating women to avoid products labeled “extra strength,” “maximum strength,” or “long-acting,” as well as combination products. Systemic decongestants also should be avoided, because human data suggest increased risk of adverse effects based on theoretically decreased fetal blood flow.²³ Oral use of phenylephrine during the first trimester has been associated with minor malformations (e.g., inguinal hernia, congenital hip dislocation).²³ Pseudoephedrine has been linked to abdominal wall defects (gastroschisis) in newborns.²³ No clear association has been found between birth defects and the use of intranasal decongestants during pregnancy.²³ Oxymetazoline is poorly absorbed after intranasal administration and is the preferred topical decongestant during pregnancy. Nonprescription cold products do not appear to affect male reproductive function.

The American Academy of Pediatrics has found pseudoephedrine to be compatible with breastfeeding.²³ No human data are available for intranasal phenylephrine and oxymetazoline, so they are considered “probably compatible” in lactating mothers.²³ Because decongestants may decrease milk production, lactating mothers should monitor their milk production and drink extra fluids as needed. Dextromethorphan, guaifenesin, benzocaine, camphor (topical), and menthol (topical) each carry a low risk of birth defects and have been found to be compatible with breastfeeding.²³

As stated earlier, older patients should be advised to use decongestants with caution, in that they may be more sensitive to adverse effects and may have a higher prevalence of concomitant disease states (e.g., cardiovascular disease)

in which nonprescription cold products may potentially have a negative impact. (See under “Special Populations” for the topic “Allergic Rhinitis” later in the chapter for a discussion of antihistamine use in the geriatric population.)

Using nonprescription cold products in children is controversial. FDA does not recommend use in children younger than 2 years because of concerns about efficacy and safety.¹² Manufacturers voluntarily updated product labeling to include the statement “Do not use in children under 4 years of age” and added warnings to antihistamine-containing products against their use for sedation purposes.¹³ However, a 2017 study showed a low incidence of adverse effects and no fatalities at therapeutic doses in children 2–11 years of age.²⁴ Patient counseling should emphasize nondrug measures in children, and if pharmacotherapy is deemed necessary, parents should follow dosing instructions carefully and avoid combination products to avoid overdose. To address the issue of inaccurate dosing of liquid nonprescription drug products (e.g., liquid analgesics, liquid cough and cold products, and lactase replacement drops), FDA issued guidelines in May 2011.²⁵ The key points of the guidelines are as follows:

- A dosing device (dropper, cup, syringe, or spoon) should be included with all oral liquid nonprescription products.
- The device should be calibrated to the dose recommended in the product directions.
- The device should be used only with the product in which it is packaged.
- The markings need to remain visible even when the liquid is in the device.

Patient Factors

As discussed earlier, it may be difficult to differentiate cold symptoms from those of some acute and chronic disorders ([Table 11–1](#)). If duration of symptoms is longer than 7–14 days or a chronic condition is suspected, self-treatment is contraindicated. Patients with chronic conditions exacerbated by adrenergic stimulation, or those overly sensitive to such stimulation, should avoid using decongestants. Persons who participate in organized sports need to be advised that oral decongestants are considered “doping” products and should be used only in accordance with sport regulations.

Patient Preferences

Lozenges, soft chews, and nasal drug delivery forms may be preferred by patients who have difficulty swallowing or when access to water is not convenient. Nasal delivery forms, however, may be difficult to use for patients with severe arthritis or coordination problems.

For patients who prefer a nasal delivery form, each dosage form has distinct advantages and disadvantages. Nasal sprays are simple to use, cover a large surface area, are relatively inexpensive, and have a fast onset of action. The disadvantages include imprecise dosage, a tendency for the tip to become clogged with repeated use, and a high risk of contamination from aspiration of nasal mucus into the bottle. Metered pump sprays deliver a more precise dose. Nasal drops are preferred for small children but can be difficult to use, cover a limited surface area, and pass easily into the larynx. A high risk of contamination stemming from the tendency to touch the dropper to the nasal mucosa during administration also is recognized. Nasal inhalers are small, but their use requires an unobstructed airway and sufficient air flow to distribute the drug to the nasal mucosa. Nasal inhalers lose efficacy after 2–3 months, even when tightly capped, because of dissipation of the active ingredient. Presence of nasal polyps, enlarged turbinates, and abnormalities such as septal deviation have been shown to be associated with reduced efficacy of topical dosage forms.

Complementary Therapies

Numerous complementary therapies are marketed for the treatment of colds (Table 11–8^{26–28}; see also Chapter 51). Zinc and high-dose vitamin C regimens are popular therapies.

Table 11–8 Selected Complementary Therapies for Colds and Allergies		
Botanical Natural Product [CAM Designation]	Risks	Effectiveness
African geranium [umckaloabo, active ingredient in Umcka ColdCare products] (<i>Pelargonium sidoides</i>)	Allergic reactions or gastrointestinal disturbances	Some evidence for alleviating symptoms of acute rhinosinusitis associated with colds in adults

Botanical Natural Product [CAM Designation]	Risks	Effectiveness
Ephedra [ma huang] (<i>Ephedra sinica</i>)	Tachycardia, hypertension, heart attack, stroke, seizure	Effective decongestant
Goldenseal (<i>Hydrastis canadensis</i>)	Potentially toxic, especially in patients with glucose-6-dehydrogenase deficiency	Some evidence of anti-inflammatory effects of active ingredient berberine for treatment of pulmonary inflammation

Key: CAM = Complementary and alternative medicine.

Source: [References 26–28](#).

High local concentrations of zinc ions purportedly block the adhesion of human rhinovirus to the nasal epithelium and also are thought to inhibit viral replication by disrupting viral capsid formation. However, in vitro studies have shown only a modest antiviral effect. Formulations include tablets, capsules, chews, lozenges, syrups, and oral sprays. Nasal formulations were removed from the market because of associated anosmia (loss of smell).²⁹ Oral formulations may be associated with GI adverse effects (e.g., nausea, upset stomach, bitter taste). Since the 1980s, the effectiveness of zinc has been highly debated. A meta-analysis of 17 trials concluded that oral zinc (as lozenges or syrup) was effective in reducing cold symptoms or duration of the cold if started within 24 hours of symptom onset and administered every 2 hours while the patient was awake. The study also reported that prophylaxis with zinc for at least 5 months reduced the incidence of colds in healthy patients.³⁰

The efficacy and safety of high-dose (e.g., ≥ 2 g daily) vitamin C (ascorbic acid) supplementation for prophylaxis and treatment of colds have been debated for more than 70 years. An analysis of 29 trials showed that although routine use of high-dose vitamin C does not appear to prevent colds in the general population, it did reduce the duration by approximately 8% in adults and 14% in children.³¹ By contrast, high-dose vitamin C prophylaxis was effective in preventing colds in a subgroup of patients under severe physical stress (e.g., marathon runners).³¹ Such use of vitamin C after the onset of a cold, however,

was not effective at reducing severity or duration of symptoms.³¹ Regular use of high doses may increase the risk of development of kidney stones in men.³² Doses of 4 g daily or greater are associated with diarrhea and other GI symptoms and therefore should not be recommended.

Products that claim to strengthen the immune system such as Airborne, Emergen-C Immune+, and others have not been proved to be effective in preventing or treating colds. Vitamin D supplementation to prevent colds is controversial, but emerging evidence suggests that regular use may prevent colds, especially in patients with low vitamin D levels.³³ Docosahexaenoic acid (DHA) supplementation during pregnancy may help to reduce the subsequent incidence and duration of colds in infants, but more studies are needed.³⁴ Homeopathic products (see also [Chapter 52](#)) containing Galphimia glauca, Sabadilla, and Luffa operculata (e.g., Zicam nasal swabs) are marketed to reduce severity if taken at the onset of symptoms, but evidence of efficacy and safety is lacking. Various probiotic products are available, and emerging research suggests that they may help support the immune system and prevent colds.³⁵ (See [Chapter 20](#) for a complete discussion of those products.)

Algorithm: The Common Cold

Figure 11–1 Self-care for the common cold. Key: AH = Antihistamine; AIDS = acquired immunodeficiency syndrome; CAM = complementary and alternative medicine; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; OTC = over-the-counter.

Assessment of Colds: A Case-Based Approach

After interviewing the patient to identify symptoms, medical history, medication use (current and past), and the efficacy of past self-treatment for colds, the health care provider should conduct a brief physical assessment ([Table 11–9](#)). If the assessment and the patient's answers do not reveal exclusions for self-treatment, the provider should recommend medications that target the patient's most troublesome symptoms.

Table 11-9 Physical Assessment of Patient Presenting With Cold Symptoms

1. Observe patient (look and listen for signs of chronic conditions, such as red, watery eyes; wheezing; productive cough; barrel chest; poorly perfused areas; enlarged lymph nodes; rash).

If equipment and privacy allow, conduct the following:

2. Obtain vital signs (temperature, respiratory rate, pulse, and blood pressure).
3. Palpate sinuses and neck, and observe for any pain/tenderness.
4. Visually examine throat for redness or exudates. If bacterial pharyngitis is suspected, run rapid strep test.
5. Auscultate chest to detect wheezing, crackles, and rapid or irregular heartbeat.

Case 11-1 is an example of assessment of a patient with a possible cold.

Case 11-1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient complains of fatigue, "runny nose," and nasal congestion that began 2 days ago. This morning, he is experiencing a mild headache in his sinus area.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	His symptoms seem to be worse at bedtime and first thing in the morning.
c. Description of the patient's efforts to relieve the symptoms	Patient tried pseudoephedrine 120 mg, which helped relieve his congestion but prevented him from sleeping. He also took ibuprofen 200 mg, 2 tablets, for the headache today.

Relevant Evaluation Criteria	Scenario/Model Outcome
d. Patient's identity	Dale Dunn
e. Patient's age, gender, height, and weight	47 years, male, 5 ft 9 in., 184 lb
f. Patient's occupation	Land surveyor
g. Patient's dietary habits	Patient eats a poor diet consisting of black coffee for breakfast, fast food for lunch, and meat and potatoes for dinner. Patient has 1–2 drinks of alcohol each night.
h. Patient's sleep habits	Normally sleeps well, except for the last few nights.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	<i>Hypertension</i> : lisinopril 20 mg daily; <i>nausea</i> : peppermint oil drops; super B complex once a day
j. Allergies	Penicillin (reaction included hives)
k. History of other adverse reactions to medications	Diarrhea with Bactrim DS
l. Other (describe) _____	Patient's temporal temperature currently is 99.6°F (37.5°C), and blood pressure is 128/86 mm Hg.
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Cold signs and symptoms usually include sore throat, nasal congestion, rhinorrhea, and low fever. Patient has nasal congestion, headache, and low-grade fever (body temperature <100.4°F [38°C]); therefore, his symptoms are consistent with a cold.
3. Identify exclusions for self-treatment (Figure 11–1).	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Recommend a combination product because the patient has multiple symptoms that are all severe. (2) Refer patient to an appropriate health

Relevant Evaluation Criteria	Scenario/Model Outcome
	care provider for evaluation and treatment. (3) Recommend self-care until patient can consult an appropriate health care provider. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Recommend self-care, and counsel patient to see an appropriate health care provider if no improvement is obtained in 7–14 days.
6. Describe the recommended therapeutic approach to the patient or caregiver.	Patient should use Afrin 0.05% (oxymetazoline) 2–3 sprays in each nostril every 12 hours. Discontinue pseudoephedrine because of the insomnia. Continue to take ibuprofen 200 mg every 4–6 hours for pain and fever; may increase to 400 mg, for a maximum of 1.2 g daily.
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"You should use Afrin for its local effects, to avoid systemic effects. Discontinue pseudoephedrine because of its unwanted side effects. Continue ibuprofen for pain and fever since it has been effective for you."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	"Use Afrin 2–3 sprays in each nostril every 12 hours. Do not use more than twice a day, and use for no more than 3 days. If it is used longer than 3 days, this medication may cause rebound congestion."
Solicit follow-up questions from the patient or caregiver.	"Do I need antibiotics for this cold?"
Answer the patient's or caregiver's questions.	"No. Colds are due to viruses, so antibiotics will not help. If the cold continues for more than 14 days, it may progress to bacterial infection, and then you

Relevant Evaluation Criteria	Scenario/Model Outcome
	may require an antibiotic.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Mr. Dunn in 1 week for checkup to ensure his symptoms have resolved.

Patient Counseling for Colds

Nondrug measures may be effective in relieving the discomfort of cold symptoms. The health care provider should explain the appropriate nondrug measures for the patient’s particular symptoms. With use of nonprescription medications, the purpose of each medication should be described, and the patient should be counseled to use only medications that target specific symptoms. Also needed is a clear explanation of possible adverse effects, drug interactions, and precautions or warnings. Finally, the health care provider should highlight the signs and symptoms that indicate the disorder is worsening and that medical care should be sought. (See the box “Patient Education for Colds.”)

Patient Education for Colds

The objectives of self-treatment are (1) to reduce symptoms, (2) to improve functioning and sense of well-being, and (3) to prevent spread of the disease. For most patients, carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

Nondrug Measures

- To prevent spreading a cold to others, follow these steps:

- Frequently wash your hands with soap for at least 20 seconds.
- Use facial tissues to cover your mouth and nose when coughing or sneezing, and then promptly discard the tissues.
- Use antiviral products such as Lysol to clean surfaces (e.g., doorknobs, telephones) that you may have touched.
- The following measures may provide relief or speed up recovery from a cold:
 - Getting adequate rest may help you recover more quickly.
 - Drinking fluids and using a humidifier or vaporizer may loosen mucus and promote sinus drainage.
 - Sucking on hard candy, gargling with salt water ($\frac{1}{2}$ –1 teaspoon of salt per 8 ounces of warm water), or drinking fruit juices or hot tea with lemon may soothe a sore throat.

Nonprescription Medications

- Ask a health care provider to help you select medications that target the most bothersome symptoms.

Sore Throat and Cough

- Sore throat may be treated with anesthetic products and/or systemic pain relievers:
 - Allow lozenges, troches, and orally disintegrating strips to dissolve slowly in the mouth; do not chew or bite these products.
 - Benzocaine and dyclonine may numb the mouth and tongue. If this occurs, do not eat or drink until the numbness goes away.
 - Seek medical attention if any of the following occur with use of benzocaine products: pale, gray- or blue-colored skin, lips, and nail beds; headache; lightheadedness; shortness of breath; fatigue; and rapid heart rate.
- Cough related to rhinorrhea leading to postnasal drip may be treated with a sedating antihistamine and decongestant

combination.

Rhinorrhea and Sneezing

- See the box “Patient Education for Allergic Rhinitis” for treatment of rhinorrhea (“runny nose”) and sneezing.

Nasal Congestion

- Nasal congestion may be treated with topical or systemic decongestants, which constrict blood vessels in the nose to reduce congestion.
 - Systemic decongestants include pseudoephedrine and phenylephrine. Dosages are listed in [Table 11-3](#).
 - Topical decongestants include ephedrine, naphazoline, oxymetazoline, phenylephrine, and xylometazoline. Dosages are listed in [Table 11-4](#).
- Decongestants have the following adverse effects:
 - The most common adverse effects caused by systemic decongestants are cardiovascular stimulation (leading to elevated blood pressure, rapid heart rate, palpitations, or arrhythmias) and central nervous system stimulation (causing restlessness, insomnia, anxiety, tremors, fear, or hallucinations).
 - Topical decongestants may cause any of the adverse effects listed for systemic decongestants. However, less of the topical medication gets into the body, so these effects are less common.
 - Topical decongestants may irritate the nose, or the bottle tip can injure the nose if it is used with inappropriate pressure.
 - Topical decongestants can cause rebound congestion if they are used longer than 3–7 days.
- Note the following precautions for use of decongestants in persons with other medical conditions:
 - Persons with high blood pressure should be advised to use decongestants only with medical advice.

- Persons with thyroid disorders, heart disease, glaucoma, or an enlarged prostate may experience worsening symptoms of their underlying disease if they take decongestants.
 - Persons with diabetes need to closely monitor their blood glucose concentrations and may need to adjust their dose of insulin if they take decongestants.
- Note the following drug interactions for decongestants:
 - Persons taking MAOI antidepressants, ergot derivatives for headaches, and certain antibiotics (linezolid) should not take decongestants.
 - Persons taking SSRI or SNRI antidepressants should be counseled to use decongestants with caution, as these medications may increase heart rate.
- Store all medications according to the manufacturer's recommendations. Do not use expired medications.

When to Seek Medical Attention

- Seek medical attention for the following situations:
 - Sore throat persists more than several days, is severe, or is associated with persistent fever, headache, or nausea or vomiting.
 - Symptoms worsen while nonprescription medications are being taken.
 - Signs and symptoms of bacterial infections develop (e.g., thick nasal or respiratory secretions that are not clear; temperature higher than 101.5°F [38.6°C; oral]; shortness of breath; chest congestion; wheezing; rash; significant ear pain).

Note About Pediatric Dosing

- Manufacturers of cough and cold medications have revised the labeling to state that these products should not be used in children younger than 4 years, and FDA has mandated that dosing devices be included with products for children older than 4 years. The

dosing device should be used only with the product in which it is packaged. Health care providers should emphasize this information to caregivers of infants and young children.

Key: FDA = U.S. Food and Drug Administration; MAOI = monoamine oxidase inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Evaluation of Patient Outcomes for Colds

Most colds are self-limiting, so symptoms usually resolve on their own in 7–14 days. For a majority of patients, targeted nonprescription therapy will relieve cold symptoms. Patients should self-monitor for worsening symptoms and progression to complications by measuring body temperature, appraising nasal secretions, assessing respirations for wheezing or shortness of breath, identifying productive cough, and ascertaining the presence and character of any facial or neck pain. If complications are suspected, medical referral is necessary. Referral to a primary care provider also is required for patients who meet the exclusions for self-treatment in [Figure 11–1](#) or for whom the warnings listed in the box “Patient Education for Colds” apply.² Follow-up assessment usually is not necessary for patients with uncomplicated colds, but a subsequent telephone call from the health care provider’s office in 7–14 days may be deemed appropriate.

Allergic Rhinitis

Allergic rhinitis, a systemic disease with prominent nasal symptoms, is a worldwide problem that affects both adults and children. An estimated 8% of adults and 10% of children in the United States are newly diagnosed with allergic rhinitis annually.³⁶ Combined annual direct costs (e.g., for medications and office visits), indirect costs (e.g., those related to work and school absenteeism), and impaired quality of life create an estimated economic burden of \$25 billion annually.³⁷

Allergic rhinitis can be diagnosed at any age but usually starts after 2 years of age.³⁸ After the age of 65 years, the number of cases decreases. The prevalence of allergic rhinitis is higher in the southern United States.³⁸

Pathophysiology of Allergic Rhinitis

Allergic rhinitis affects the upper respiratory system. (The previous topic, “Colds,” includes a detailed discussion of the respiratory anatomy and physiology.) Risk factors for developing allergic rhinitis include family history of atopy (allergic disorders) in one or both parents; filaggrin (skin barrier protein) gene mutation; elevated serum immunoglobulin E (IgE) greater than 100 IU/mL before the age of 6 years; higher socioeconomic level; eczema; and positive reaction to allergy skin tests.^{39,40} Emerging evidence also suggests that diet may be a risk factor in children and adolescents. Children who consume three or more fast-food meals per week showed an increased incidence of allergic disorders.⁴¹ The exact mechanism for that increase is not known but is thought to be related to higher dietary content of fatty acids, especially trans fatty acids, which trigger an immune response.⁴¹

Allergic rhinitis is triggered by indoor and outdoor environmental allergens. Common outdoor aeroallergens (airborne environmental allergens) include pollen and mold spores. Other nonairborne pollens also have been implicated. Pollutants (e.g., ozone, tobacco smoke, diesel exhaust particles) are considered environmental triggers and are becoming more of a concern in highly populated areas. Common indoor aeroallergens include those from house-dust mites and cockroaches, mold spores, and pet dander. Occupational aeroallergens include wool dust, latex, resins, biologic enzymes, organic dusts (e.g., flour), and various chemicals (e.g., isocyanate, glutaraldehyde).

The pathogenesis of allergic rhinitis is complex, involving numerous cells and mediators, and consists of four phases.⁴² First is the *sensitization phase*, which occurs on initial allergen exposure. The allergen stimulates beta-lymphocyte-mediated IgE production. Second is the *early phase*, occurring within minutes of subsequent allergen exposure. The early phase consists of rapid release of preformed mast cell mediators (e.g., histamine, proteases), as well as the production of additional mediators (e.g., prostaglandins, kinins, leukotrienes, neuropeptides). [Figure 11–2](#) depicts the emergence of mediator-specific symptoms. The third phase is *cellular recruitment*. Circulating

leukocytes, especially eosinophils, are attracted to the nasal mucosa and release more inflammatory mediators. Fourth and last is the *late phase*, which begins 2–4 hours after allergen exposure; signs and symptoms include mucus hypersecretion secondary to submucosal gland hypertrophy and congestion. Continued persistent inflammation “primes” the tissue, resulting in a lower threshold for allergic- and nonallergic-mediated triggers (e.g., cold air, strong odors).

Algorithm: Mediator-specific symptoms

Figure 11–2 Mediator-specific symptoms and targeted drug therapy. Key: IgE = Immunoglobulin E; INCS = intranasal corticosteroids; PGD = prostaglandin. (Source: [Reference 42](#).)

Clinical Presentation of Allergic Rhinitis

Allergic rhinitis has been classified as seasonal allergic rhinitis (“hay fever”) and perennial allergic rhinitis. Allergic rhinitis is further classified as *episodic*, *intermittent* allergic rhinitis (IAR) and *persistent* allergic rhinitis (PER).^{39,40} Classification depends on the timing and duration of symptoms. Symptoms can be further classified as mild or moderate to severe ([Table 11–10](#)).^{39,40} Symptoms of allergic rhinitis and common physical findings in affected patients are summarized in [Table 11–11](#)^{39,40,42} and can be used to differentiate allergic from nonallergic rhinitis. [Table 11–12](#) lists causes of nonallergic rhinitis.^{39,40,42} Systemic symptoms include fatigue, irritability, malaise, and cognitive impairment.

Table 11–10 Classification of Allergic Rhinitis	
Duration	Severity
Intermittent	Mild
Symptoms occur ≤4 days per week or ≤4 weeks.	Symptoms do not impair sleep or daily activities ^a ; no troublesome symptoms.
	Moderate–Severe

Duration	Severity
	One or more of the following occurs: impairment of sleep; impairment of daily activities ^a ; troublesome symptoms.
Persistent	Mild
Symptoms occur <4 days per week <i>and</i> <4 weeks.	Symptoms do not impair sleep or daily activities ^a ; no troublesome symptoms.
	Moderate–Severe
	One or more of the following occurs: impairment of sleep; impairment of daily activities ^a ; troublesome symptoms.
Episodic	
Symptoms occur on exposure to or contact with potential allergen that is not normally a part of the person's environment (e.g., a cat at a friend's house).	Can be mild, moderate, or severe—based on symptoms

^a Daily activities include work, school, sports, and leisure.

Source: [References 39](#) and [40](#).

Table 11–11 Differentiation of Allergic Rhinitis From Nonallergic Rhinitis

Symptoms/Findings	Allergic Rhinitis	Nonallergic Rhinitis^a
Symptom presentation	Bilateral symptoms that are worst upon awakening, subside during the day, then may worsen at night	Unilateral symptoms common but can be bilateral; constant day and night
Sneezing	Frequent, paroxysmal	Little or none
Rhinorrhea	Anterior, watery	Posterior, watery or thick and/or mucopurulent (associated with an infection)
Pruritus (itching) of eyes, nose, and/or palate	Frequent	Not present

Symptoms/Findings	Allergic Rhinitis	Nonallergic Rhinitis^a
Nasal obstruction	Variable	Usually present and often severe
Conjunctivitis (red, irritated eyes with prominent conjunctival blood vessels)	Frequent	Not present
Pain	Sinus pain due to congestion may be present; throat pain due to postnasal drip irritation may be present.	Variable depending on cause
Anosmia	Rare	Frequent
Epistaxis	Rare	Recurrent
Facial, nasal, or throat features	“Allergic shiners” (periorbital darkening secondary to venous congestion)	Nasal polyps Nasal septal deviation Enlarged tonsils and/or adenoids
	“Dennie’s lines” (wrinkles beneath the lower eyelids)	
	“Allergic crease” (horizontal crease just above bulbar portion of the nose secondary to the “allergic salute”)	
	“Allergic salute” (upward “swipe” of tip of the nose with palm of the hand)	
	“Allergic gape” (open-mouth breathing secondary to nasal obstruction)	
	Nonexudative “cobblestone” appearance of posterior oropharynx	

^a Depending on the cause of the nonallergic rhinitis, not all signs and symptoms may be present.

Source: [References 39](#) and [42](#).

Table 11-12 Causes of Nonallergic Rhinitis

Hormonal	Systemic Inflammatory
Pregnancy, puberty, thyroid disorders	Eosinophilic nonallergic rhinitis (NARES)
Structural	Lesions
Septal deviation, adenoid hypertrophy	Nasal polyps, neoplasms
Drug-Induced	Traumatic
Cocaine, beta blockers, ACEIs, chlorpromazine, clonidine, reserpine, hydralazine, oral contraceptives, aspirin or other NSAIDs, overuse of topical decongestants	Recent facial or head trauma
	Autonomic (Vasomotor)
	Age-related; physical or chemical agent causing parasympathetic hyperactivity

Key: ACEIs = Angiotensin-converting enzyme inhibitors; NARES = nonallergic rhinitis with eosinophilia syndrome; NSAIDs = nonsteroidal anti-inflammatory drugs.

Source: [Reference 42](#).

Acute complications of allergic rhinitis include sinusitis and otitis media with effusion. Complications of a chronic nature include nasal polyp formation, sleep apnea, sinusitis, and hyposmia (diminished sense of smell).^{37,39,40} Allergic rhinitis and asthma share a common pathology, and allergic rhinitis has been implicated in the development of asthma and in exacerbations of preexisting asthma in children and adults. Depression, anxiety, sexual dysfunction, delayed speech development, and facial or dental abnormalities also have been linked to allergic rhinitis.^{37,39,40}

Algorithm: Allergic Rhinitis

Figure 11–3 Self-care for allergic rhinitis. Key: ADR = Adverse drug reaction; AH = antihistamine; AR = allergic rhinitis; COPD = chronic obstructive pulmonary disease; HCP = health care provider; IAR = intermittent allergic rhinitis; INCS = intranasal corticosteroids; PER = persistent allergic rhinitis; Rx = prescription.

Treatment of Allergic Rhinitis

Treatment Goals

Allergic rhinitis cannot be cured. The goals of therapy are to reduce symptoms and to improve the patient's functional status and sense of well-being. Treatment is individualized to provide optimal symptomatic relief and/or control.

General Treatment Approach

Allergic rhinitis is treated in three steps: allergen avoidance, pharmacotherapy, and immunotherapy.^{39,40,42} Patient education is an important part of all three steps, especially regarding continuous allergen avoidance and the administration of nonprescription medications (for instructions, see [Table 11–2](#) for intranasal preparations and [Chapter 28](#), “Ophthalmic Disorders,” for ophthalmic drugs). The algorithm in [Figure 11–3](#) outlines the self-treatment approach for episodic allergic rhinitis, IAR, and PER and lists exclusions for self-treatment.^{39,40} Because allergen avoidance alone typically is not sufficient to provide complete relief in allergic rhinitis, targeted therapy with single-entity drugs is usually initiated. Nonprescription therapy with intranasal corticosteroids (INCS), antihistamines, or decongestants usually can control most symptoms. Agents with different mechanisms of action or delivery systems may be added if single-drug therapy does not provide adequate relief, or if symptoms are already moderately severe, particularly intense, or long-lasting.

Nonpharmacologic Therapy

Allergen avoidance is the primary nonpharmacologic measure for

management of allergic rhinitis. Avoidance strategies depend on the specific allergen. House-dust mites (*Dermatophagoides* spp.), found in all but the driest regions of the United States, thrive in warm, humid environments. The main allergen is a fecal glycoprotein, but other mite proteins and proteases also are allergenic. Avoidance strategies, targeted at reducing the mite population, include lowering the household humidity to less than 40%, applying acaricides, and reducing mite-harboring dust by removing carpets, upholstered furniture, stuffed animals, and bookshelves from the patient's bedroom and other rooms if possible. Mite populations in bedding are reduced by encasing the mattress, box springs, and pillows with mite-impermeable materials. Bedding should be washed at least weekly in hot (131°F [55°C]) water.

Outdoor mold spores are prevalent in late summer and fall, especially on calm, clear, dry days. *Alternaria* and *Cladosporium* are common outdoor allergenic molds; *Penicillium* and *Aspergillus* are common indoor molds. Avoiding activities that disturb decaying plant material (e.g., raking leaves) lessens exposure to outdoor mold. Indoor mold exposure is minimized by lowering household humidity, removing houseplants, venting food preparation areas and bathrooms, repairing damp basements or crawl spaces, and frequently applying fungicide to obviously moldy areas.

Cat-derived allergens (the Fel d1 family of proteins, secreted through sebaceous glands in the skin) are small and light, and they stay airborne for several hours. Cat allergens can be found in the home months after the pet is removed. Although of unproven benefit, weekly cat baths may reduce the allergen load.

Cockroaches are a major source of urban allergens; their saliva, feces, and body parts all have been implicated. To eliminate cockroaches, patients should be encouraged to keep kitchen areas clean, to keep stored food tightly sealed, and to treat infested areas with baits or pesticides.

Pollutants (e.g., ozone, diesel fumes) are an additional concern in urban environments. Pollutants such as diesel exhaust particles are especially irritating to the respiratory tract and have been shown to increase the severity of allergic rhinitis.^{39,40} Patients whose allergies are triggered by air pollutants should be aware of the air quality index (AQI)—a measure of five major air pollutants per 24 hours—and should plan outdoor activities when the AQI is low.

In general, trees produce pollen in spring, grasses in early summer, and ragweed from mid-August to the first fall frost. Knowledge of pollen counts (the number of pollen grains per cubic meter per 24 hours) will help patients plan outdoor activities. Most patients are symptomatic when pollen counts are very high, and only very sensitive patients have symptoms when pollen counts are low. Pollen counts are highest early in the morning and lowest after rainstorms clear the air. Avoiding outdoor activities when pollen counts are high and closing house and car windows will reduce pollen exposure.

Ventilation systems with high-efficiency particulate air (HEPA) filters remove pollen, mold spores, and cat allergens from household air but not fecal particles from house-dust mites, which settle to the floor too quickly to be filtered. Filters need to be changed regularly to maintain effectiveness. The systems are expensive and not effective for all patients. HEPA filters also are found in some vacuum cleaners. Weekly vacuuming of carpets, drapes, and upholstery with a HEPA filter–equipped vacuum cleaner may help reduce household allergens, including those from house-dust mites.⁴²

Use of nasal wetting agents (e.g., saline, propylene, polyethylene glycol sprays, gels) or nasal irrigation with warm saline (isotonic or hypertonic) delivered using a syringe or Neti pot may relieve nasal mucosal irritation and dryness, thus decreasing nasal stuffiness, rhinorrhea, and sneezing. These measures also aid in the removal of dried, encrusted, or thick mucus from the nose. No significant adverse effects have been noted with use of nasal wetting agents. Mild stinging or burning has been noted with saline irrigation. Only distilled, sterile, or boiled tap water should be used to prepare nasal irrigation solutions because of the risk of rare but serious infections.

Pharmacologic Therapy

INCS regimens have been shown to be the most effective treatment for most symptoms of allergic rhinitis.^{39,40,42} Other nonprescription options include ocular and oral antihistamines, topical and oral decongestants, and mast cell stabilizers. Patients should start taking INCS, antihistamines, and mast cell stabilizers at least 1 week before symptoms typically appear or as soon as possible before expected allergen exposures. Length of the therapeutic course for these medications should be individualized according to duration and severity of symptoms, pattern of allergen exposure (episodic or continuous), and geographic location.

Intranasal Corticosteroids

INCS, also known as glucocorticoids, are very effective agents for treatment of nasal symptoms such as itching, rhinitis, sneezing, and congestion, because they inhibit multiple cell types and mediators, including histamine, and effectively stop the “allergic cascade.”^{39,40} Budesonide, fluticasone furoate, fluticasone propionate, and triamcinolone acetonide are FDA approved for nonprescription use for nasal symptoms.⁴³ Fluticasone furoate and fluticasone propionate have additional FDA approval status for nonprescription use to treat ophthalmic symptoms such as itchy or watery eyes.⁴³ FDA-approved dosages for INCS are listed in [Table 11–13](#).⁴³

Table 11–13 Nonprescription Intranasal Corticosteroid Products and Dosage Guidelines

Drug	Brand Name	Strength	Dosage ^a
Budesonide	Rhinocort Allergy Spray	32 mcg/spray	<i>Adults and children ≥ 12 years:</i> Use 2 sprays in each nostril once daily; once allergy symptoms improve, reduce to 1 spray in each nostril per day.
			<i>Children 6–11 years:</i> Use 1 spray in each nostril once daily; if allergy symptoms do not improve, may increase to 2 sprays in each nostril per day. Once allergy symptoms improve, reduce to 1 spray in each nostril per day.
			<i>Children < 6 years:</i> Do not use.
Fluticasone furoate	Flonase Sensimist	27.5 mcg/spray	<i>Adults and children ≥ 12 years:</i> Week 1: Use 2 sprays in each nostril once daily. Weeks 2–26: Use 1 or 2 sprays in each nostril once daily. After 26 weeks of daily use without improvement, consult appropriate HCP.
	Children's Flonase Sensimist		<i>Children 2–11 years:</i> Use 1 spray in each nostril once daily. After 8 weeks of daily use without improvement, consult appropriate HCP.
			<i>Child < 2 years:</i> Do not use.
Fluticasone propionate	Flonase Allergy Relief	50 mcg/spray	<i>Adults and children ≥ 12 years:</i> Week 1: Use 2 sprays in each nostril once daily. Weeks 2–26: Use 1 or 2 sprays in each nostril once daily. After 26 weeks of daily use without improvement, consult appropriate HCP.

Drug	Brand Name	Strength	Dosage ^a
	Children's Flonase Allergy Relief		<i>Children 4–11 years:</i> Use 1 spray in each nostril once daily. For persistent symptoms after 8 weeks of daily use, consult appropriate HCP.
			<i>Child < 4 years:</i> Do not use.
Triamcinolone acetonide	Nasacort Allergy 24HR	55 mcg/spray	<i>Adults and children ≥ 12 years:</i> Use 2 sprays in each nostril once daily; once allergy symptoms decrease, reduce to 1 spray in each nostril per day.
	Children's Nasacort Allergy 24HR		<i>Children 6–11 years:</i> Use 1 spray in each nostril once daily; if allergy symptoms do not subside, may increase to 2 sprays in each nostril per day. Once allergy symptoms decrease, reduce to 1 spray in each nostril per day.
			<i>Children 25 years:</i> Use 1 spray in each nostril once daily.
			<i>Children < 2 years:</i> Do not use.

^a Patients should be instructed to shake bottle before use to ensure suspension is mixed and uniform.

Key: HCP = Health care provider.

Source: [Reference 43](#).

INCS usually are well tolerated. Adverse effects typically are minor and include nasal discomfort or bleeding, sneezing, cough, and pharyngitis. INCS exhibit variable systemic absorption (e.g., fluticasone <2% versus budesonide 34%). Patients who are sensitive to INCS or who use higher-than-recommended doses may experience systemic effects such as headache, dizziness, nausea, and vomiting. Additionally, long-term use has been linked to changes in vision, glaucoma, cataract formation, increased risk of infection (e.g., *Candida*), and growth inhibition in children. INCS have few drug interactions, as listed in [Table 11–6](#).

Antihistamines

Since the 1940s, antihistamines have been used to treat allergies.^{39,40} These drugs are classified as sedating (first-generation, nonselective) or nonsedating (second-generation, peripherally selective). The role of sedating antihistamines in treating allergic rhinitis is controversial. Sedating antihistamines are effective, readily available without a prescription, and relatively inexpensive. However, these antihistamines expose patients to risks associated with their anticholinergic effects and should be used with caution.

Antihistamines compete with histamine at central and peripheral histamine type 1 (H₁) receptor sites, preventing the histamine receptor interaction and subsequent mediator release. In addition, second-generation antihistamines inhibit the release of mast cell mediators and may decrease cellular recruitment.

Differences among antihistamines relate to the rapidity and degree to which they penetrate the blood–brain barrier as well as to their receptor specificity. Sedating antihistamines are highly lipophilic molecules that readily cross the blood–brain barrier. Nonsedating antihistamines are large protein-bound lipophobic molecules with charged side chains that reduce their ability to cross the blood–brain barrier. Both types of antihistamines are highly selective for H₁ receptors but have little effect on H₂, H₃, or H₄ receptors. The sedating antihistamines have anticholinergic, antiserotonin, and anti- α -adrenergic effects.

Each antihistamine chemical class (Table 11-14) differs slightly in terms of its activity and adverse effect profile.^{44,45} Most sedating antihistamines are well absorbed after oral administration, with time to peak plasma concentrations in the range of 1.5–3 hours. Protein binding is in the range of 78%–99%, and sedating antihistamines undergo significant first-pass metabolism through the cytochrome P450 system. Half-lives vary widely—for example, 2–10 hours for diphenhydramine versus 20–24 hours for chlorpheniramine.

Table 11-14 Antihistamine Classes

Class With Specific Drug Entities	Properties
Alkylamines: brompheniramine, chlorpheniramine,	Moderately sedating; strong anticholinergic effects; higher risk of paradoxical CNS stimulation than with

Class With Specific Drug Entities	Properties
dexbrompheniramine, dexchlorpheniramine, pheniramine, triprolidine	other classes
Ethanolamines: diphenhydramine, doxylamine	Highly sedating; strong anticholinergic effects; with large doses, risk for seizures and arrhythmias
Ethylenediamines: pyrilamine, thonzylamine	Weak CNS effects; increased GI effects
Phenothiazines: promethazine	Highly sedating; strong anticholinergic effects; block alpha-adrenergic receptors; more likely to cause hypotension; other potential effects: akathisia and dystonic reactions
Piperidines: fexofenadine, loratadine	Nonsedating
Piperazines: cetirizine, chlorcyclizine, hydroxyzine, levocetirizine, meclizine	Minimally to moderately sedating

Key: CNS = Central nervous system; GI = gastrointestinal.

Source: [References 44](#) and [45](#).

The nonsedating antihistamines are also rapidly absorbed after oral administration, with time to peak plasma concentrations in the range of 1–3 hours. Loratadine has the highest protein binding at 97% and is extensively metabolized by the liver to an active metabolite (desloratadine), whereas cetirizine, fexofenadine, and levocetirizine are minimally metabolized. Half-lives range from 8 hours (for cetirizine, levocetirizine, loratadine) to 14 hours (for fexofenadine).

Antihistamines are indicated for relief of symptoms of allergic rhinitis (e.g., itching, sneezing, rhinorrhea) and other types of immediate hypersensitivity reactions. FDA-approved dosages for systemic antihistamines are listed in [Table 11–15](#).¹¹ Nonprescription antihistamines are marketed as immediate-release and sustained-release tablets and capsules, chewable tablets, oral disintegrating tablets, solutions, and syrups. Alcohol-free, sucrose-free, and

dye-free formulations are available. (See [Chapter 28](#) for a discussion of ophthalmic antihistamines.)

Table 11-15 Dosage Guidelines for Systemic Nonprescription Antihistamines

Drug	Dosage ^a (maximum daily dosage)		
	Adults/Children ≥ 12 Years	Children 6 to < 12 Years	Children 2 to < 6 Years ^b
Brompheniramine maleate	4 mg every 4–6 hours (24 mg)	2 mg every 4–6 hours (12 mg)	1 mg every 4–6 hours (6 mg)
Cetirizine HCl ^c	10 mg every 24 hours (10 mg)	5–10 mg every 24 hours (10 mg)	2.5 mg every 12 hours or 2.5–5.0 mg every 24 hours (5 mg)
Chlorcyclizine HCl ^d	25 mg every 6–8 hours (75 mg)	Not recommended for children <12 years except under advice of HCP	–
Chlorpheniramine maleate	4 mg every 4–6 hours (24 mg)	2 mg every 4–6 hours (12 mg)	1 mg every 4–6 hours (6 mg)
Dexbrompheniramine maleate	2 mg every 4–6 hours (12 mg)	1 mg every 4–6 hours (6 mg)	0.5 mg every 4–6 hours (3 mg)
Dexchlorpheniramine maleate	2 mg every 4–6 hours (12 mg)	1 mg every 4–6 hours (6 mg)	0.5 mg every 4–6 hours (3 mg)
Diphenhydramine citrate	38–76 mg every 4–6 hours (456 mg)	19–38 mg every 4–6 hours (228 mg)	9.5 mg every 4–6 hours (57 mg)
Diphenhydramine HCl	25–50 mg every 4–6 hours (300 mg)	12.5–25 mg every 4–6 hours (150 mg)	6.25 mg every 4–6 hours (37.5 mg)
Doxylamine succinate	7.5–12.5 mg every 4–6 hours (75 mg)	3.75–6.25 mg every 4–6 hours (37.5 mg)	1.9–3.125 mg every 4–6 hours (18.75 mg)
Fexofenadine ^e	60 mg every 12 hours or 180 mg every 24 hours (180 mg)	30 mg every 12 hours (60 mg)	30 mg every 12 hours (60 mg)
Levocetirizine ^e	5 mg every 24 hours (5 mg)	2.5 mg every 24 hours (2.5 mg)	1.25 mg every 24 hours (1.25 mg)
Loratadine	10 mg every 24	10 mg every 24 hours (10	5 mg every 24 hours

Drug	Dosage ^a (maximum daily dosage)		
	Adults/Children ≥ 12 Years	Children 6 to < 12 Years	Children 2 to < 6 Years ^b
	hours (10 mg)	mg)	(5 mg)
Phenindamine tartrate ^d	25 mg every 4–6 hours (150 mg)	12.5 mg every 4–6 hours (75 mg)	6.25 mg every 4–6 hours (37.5 mg)
Pheniramine maleate	12.5–25 mg every 4–6 hours (150 mg)	6.25–12.5 mg every 4–6 hours (75 mg)	3.125–6.25 mg every 4–6 hours (37.5 mg)
Pyrilamine maleate	25–50 mg every 6–8 hours (200 mg)	12.5–25 mg every 6–8 hours (100 mg)	6.25–12.5 mg every 6–8 hours (50 mg)
Thonzylamine HCl ^d	50–100 mg every 4–6 hours (600 mg)	25–50 mg every 4–6 hours (300 mg)	12.5–25.0 mg every 4–6 hours (150 mg)
Tripolidine HCl ^d	2.5 mg every 4–6 hours (10 mg)	1.25 mg every 4–6 hours (5 mg)	Age 4–6 years: 0.938 mg every 4–6 hours (3.744 mg)
			Age 2 to <4 years: 0.625 mg every 4–6 hours (2.5 mg)
			Age 4 months to <2 years: 0.313 mg every 4–6 hours (1.25 mg)

^a Taken as needed.

^b With the exception of cetirizine, fexofenadine, levocetirizine, and loratadine, these products are not recommended for children younger than 6 years, except with the advice and supervision of an HCP. FDA recommends that the labels on nonprescription products not provide dosing information for children younger than 6 years.

^c For adults older than 65 years, 10 mg cetirizine is not recommended, except with the advice and supervision of an HCP.

^d Drug is FDA approved but not currently marketed in the United States.

^e For adults older than 65 years, fexofenadine and levocetirizine are not recommended,

except with the advice and supervision of an HCP.

Key: FDA = U.S. Food and Drug Administration; HCP = health care provider.

Source: [Reference 11](#).

Sedating antihistamine overdoses are characterized by excessive H₁, cholinergic, alpha-adrenergic, and serotonergic receptor blockade.⁴⁵ Overdoses also cause excessive blockade of fast sodium channels and potassium channels, leading to cardiac symptoms (tachycardia and conduction abnormalities, including torsades de pointes).⁴⁵ CNS signs and symptoms include toxic psychosis, hallucinations, agitation, lethargy, tremor, insomnia, and tonic-clonic seizures. Children tend to be more sensitive to CNS excitatory effects, and adults are more likely to experience CNS depression.⁴⁵ Peripheral signs and symptoms include hyperpyrexia, mydriasis, vasodilation, decreased exocrine secretion, urinary retention, decreased GI motility, dystonic reactions, and rhabdomyolysis. Overdoses of nonsedating antihistamines are characterized by drowsiness, restlessness/hyperactivity, and tachycardia. Treatment of antihistamine overdoses is supportive.

The adverse effect profile of systemic antihistamines varies widely and depends on the receptor activity, chemical structure, and lipophilicity of the specific drug. The primary adverse effects, CNS effects (depression and stimulation) and anticholinergic effects, are common with first-generation antihistamines but are rarely seen with second-generation agents. CNS-depressive effects include sedation and impaired performance (e.g., impaired driving performance, poor work performance, incoordination, reduced motor skills, and impaired information processing).⁴⁵ CNS-stimulatory effects include anxiety, hallucinations, appetite stimulation, muscle dyskinesias, and activation of epileptogenic foci. Adverse effects associated with cholinergic blockage include dryness of the eyes and mucous membranes (mouth, nose, vagina), blurred vision, urinary hesitancy and retention, constipation, and reflex tachycardia. Skin eruptions may occur with use of second-generation antihistamines, especially in children. If such lesions appear, antihistamines should be stopped and subsequently reintroduced to establish or exclude an association.

Antihistamines interact with numerous drugs ([Table 11–6](#)).⁴⁴ All antihistamines decrease or prevent immediate dermal reactivity and should be discontinued at least 4 days before scheduled allergy skin testing. Fexofenadine should not be taken with any fruit juices (e.g., grapefruit, apple, orange). Fruit juice is thought to reduce absorption of fexofenadine by directly inhibiting intestinal organic anion–transporting polypeptides (OATPs), specifically OATP1A2.⁴⁶ Separating fexofenadine dose and fruit juice consumption by at least 2 hours will avoid this interaction.⁴⁶

Sedating antihistamines are contraindicated in newborns or premature infants, lactating women, and patients with narrow-angle glaucoma. Additional contraindications include acute asthma exacerbation, stenosing peptic ulcer, symptomatic prostatic hypertrophy, bladder neck and pyloroduodenal obstruction, and concomitant use of MAOIs. Formulations of 12- and 24-hour sustained-release loratadine/pseudoephedrine combination products are contraindicated in patients with esophageal narrowing, abnormal esophageal peristalsis, or a history of difficulty swallowing tablets.

In patients with lower respiratory tract diseases (e.g., emphysema, chronic bronchitis), caution is recommended with use of sedating antihistamines. People whose activities require mental alertness should not use sedating antihistamines and should be advised to use levocetirizine and cetirizine with caution. Function may be impaired even if the patient does not feel drowsy or took the dose the previous evening. The sedating antihistamines are photosensitizing drugs. Patients should be advised to use sunscreen and to wear protective clothing.

Combination Antihistamine Products

Antihistamines are marketed in combination with decongestants and analgesics. Those combinations are also available in sustained-release formulations, allowing convenient dosage regimens. These combination products should be used with caution, however, because of the increased risk of adverse effects, especially insomnia, which compounds the daytime fatigue already associated with allergic rhinitis.

Decongestants

Congestion is a common allergic rhinitis symptom controllable with systemic decongestants or with short-term (~5 days) use of topical nasal decongestants.

Patients with allergic rhinitis may also have mild intermittent asthma symptoms such as wheezing, chest tightness, and shortness of breath. Besides its decongestant properties, epinephrine is also a bronchodilator and is available as an oral inhaler (Primatene Mist), which delivers 0.125 mg/spray. The inhaler is FDA approved for temporary relief of symptoms in patients older than 12 years of age who have already been diagnosed with asthma by a medical provider. Patients may use 1–2 sprays every 4 hours, up to a maximum of 8 sprays in 24 hours. Patients should seek medical care or further evaluation if symptoms are not relieved in 20 minutes or worsen after use, or if they experience more than two exacerbations per week. (See earlier discussion of decongestants for the topic “Colds.”)

Cromolyn Sodium

Cromolyn is a mast cell stabilizer indicated for preventing and treating the symptoms of allergic rhinitis. Cromolyn is thought to work by blocking the influx of calcium into mast cells, thereby preventing mediator release. Less than 7% of an intranasal cromolyn dose is absorbed systemically, and what little is absorbed has no systemic activity. The absorbed drug is rapidly excreted unchanged in the feces and urine, with a half-life of 1–2 hours.

Cromolyn is approved for use in patients 2 years of age or older; the recommended dosage is 1 spray in each nostril 3–6 times daily at regular intervals.¹¹ Treatment is more effective if started before symptoms begin. It may take 3–7 days for initial clinical improvement to become apparent and 2–4 weeks of continued therapy to achieve maximal therapeutic benefit. Sneezing is the most common adverse effect reported for intranasal cromolyn. Other adverse effects include nasal stinging and burning. No drug interactions have been reported with intranasal cromolyn.

Pharmacotherapeutic Comparison

INCS have been shown to be the most effective agents for treatment of moderate to severe IAR and both types of PER. Monotherapy with INCS is considered first-line treatment.^{39,40,42} If additional symptom control is needed, combination therapy with antihistamines, decongestants, or mast cell stabilizers can be initiated. Owing to their quick onset of action, oral antihistamines are first-choice agents for symptom control in episodic allergic rhinitis. Both sedating and nonsedating antihistamines are effective. Some

evidence suggests greater efficacy for the sedating type in treating symptoms of allergic rhinitis.⁴⁷ However, this evidence is based on trials using the maximum daily dosage (50 mg) of diphenhydramine.⁴⁷ Sedating antihistamines have a rapid onset of action, but the duration of action also is shorter, and multiple daily doses are required. The risks of cognition impairment and sedation have been well established with this class of drugs.⁴⁵ The World Health Organization strongly recommends nonsedating antihistamines on the basis of their efficacy and safety profile, quick onset of action, and longer duration, which allows once-daily dosing.^{39,46}

Cetirizine has been shown to be a more potent antihistamine than either loratadine or fexofenadine.⁴⁶ However, it is more likely to cause sedation (occurring in approximately 10% of patients).

Product Selection Guidelines

Special Populations

Because pregnancy is a common cause of nonallergic rhinitis, pregnant women should be referred for differential diagnosis. If allergic rhinitis is confirmed and nonprescription therapy is approved by a primary care provider, several treatment choices are available.²³ (Please refer to the Preface for a detailed explanation of the pregnancy data.) Intranasal cromolyn is considered compatible with pregnancy and is a first-line option.²³ Diphenhydramine and chlorpheniramine also are considered compatible with pregnancy.²³ Levocetirizine, loratadine, and cetirizine are considered to carry a low risk for adverse fetal effects, whereas fexofenadine is associated with moderate risk.²³ INCS are considered compatible with pregnancy. However, systemic use of budesonide and triamcinolone has been linked to cleft lip and palate and low birth weight.²³ Nonprescription allergy products do not appear to affect male reproductive function.

Lactating women diagnosed with allergic rhinitis and approved for self-treatment by a primary care provider have fewer options. Because of its limited systemic absorption, intranasal cromolyn is a good choice, and adverse effects in nursing infants have not been reported.²³ INCS are low-molecular-weight molecules and are thought to be excreted in breast milk. Reports of INCS causing harm in nursing infants are lacking, however, and they are considered “probably compatible.”²³ Antihistamines are contraindicated during lactation

because of their ability to pass into breast milk. Short-acting chlorpheniramine, fexofenadine, or loratadine seems to be the best option if an oral antihistamine is needed, but such medication should be used with caution and under the supervision of a primary care provider. If an oral antihistamine is used during lactation, the mother should avoid long-acting and high-dose antihistamines and should take the dose at bedtime after the last feeding of the day.²³

Because of concerns regarding undiagnosed asthma, children younger than 12 years should be referred to a primary care provider for differential diagnosis.^{39,40} If nonprescription therapy is approved by a primary care provider, several treatment choices are available for children.^{39,40,46} Intranasal cromolyn, fluticasone furoate, and triamcinolone acetonide are safe for children 2 years of age and older, intranasal fluticasone propionate is safe for children 4 years and older, and intranasal budesonide is safe for children 6 years and older. However, these products may be difficult for children to self-administer. In addition, all three INCS have been linked to growth inhibition in children; FDA-mandated labeling for the nonprescription products encourages parents to speak to an appropriate health care provider if they plan to use these products in children for longer than 2 months per year.⁴³ Loratadine is the nonprescription antihistamine of choice, followed by fexofenadine, levocetirizine, and cetirizine. Sedating antihistamines should be avoided in children because of paradoxical excitation and risk for serious adverse events with misuse.⁴⁶

Sedating antihistamines should be avoided in older patients because they are more likely than younger adults to be taking concomitant medications with anticholinergic properties and are at increased risk for CNS-depressive adverse effects, including confusion as well as hypotension.⁴⁸ Those adverse effects contribute to a higher risk of falling in this population.⁴⁸ Loratadine and intranasal cromolyn are drugs of choice in older patients. Dosage of fexofenadine and levocetirizine should be adjusted in patients with renal impairment. Loratadine and cetirizine dosage should be adjusted in patients with renal and/or hepatic impairment.

Patient Factors and Preferences

The duration of treatment and the presence of concomitant symptoms will determine which antihistamine product is selected ([Table 11-16](#)). Product selection also may be based on adverse effect profiles and cost. For example,

all first-generation antihistamines are sedating, but the degree of sedation depends on chemical class ([Table 11-14](#)). Nonsedating antihistamines are more expensive but carry less risk of sedation and impairment, which may justify the additional cost. Some patients report that antihistamines are less effective after prolonged use. This decline is most likely not indicative of true tolerance but rather stems from several factors, including patient nonadherence to dosing regimens, an increase in antigen exposure, worsening of disease, limited effectiveness of antihistamines in severe disease, and the development of similar symptoms from unrelated diseases. Chemical class differences make it reasonable to suggest switching to a different class of antihistamine if the patient has a less-than-optimal response to a specific antihistamine agent. Patient sensory perception of INCS characteristics also may influence therapy. Alcohol-free formulations may be preferred by patients who are sensitive to smell, taste, or aftertaste of nasal preparations.

Table 11-16 Selected Nonprescription Products for Allergic Rhinitis

Trade Name	Primary Ingredient(s)
Systemic First-Generation Antihistamine Products	
Chlor-Trimeton Allergy (4, 8, or 12 Hour) Tablets	Chlorpheniramine 4, 8, or 12 mg, respectively
Benadryl Allergy Tablets	Diphenhydramine HCl 25 mg
Children's Benadryl Allergy Liquid	Diphenhydramine HCl 12.5 mg/5 mL
Systemic Second-Generation Antihistamine Products	
Zyrtec Tablets	Cetirizine 10 mg
Children's Zyrtec Allergy Syrup	Cetirizine 5 mg/5 mL
Allegra Allergy 24 hour Tablets	Fexofenadine 180 mg
Children's Allegra Meltable Tablets	Fexofenadine 30 mg
Xyzal Allergy 24HR Tablets	Levocetirizine 5 mg
Children's Xyzal Allergy 24HR Oral Solution	Levocetirizine 2.5 mg/5 mL
Claritin Non-Drowsy Tablets	Loratadine 10 mg

Trade Name	Primary Ingredient(s)
Alavert Allergy Orally Disintegrating Tablets	Loratadine 10 mg
Combination Systemic Products	
Children's Dimetapp Cold and Allergy	Brompheniramine 1 mg/5 mL; phenylephrine 2.5 mg/5 mL
Zyrtec D Tablets	Cetirizine 5 mg; pseudoephedrine HCl 120 mg
Advil Allergy Sinus Caplets	Chlorpheniramine 2 mg; pseudoephedrine HCl 30 mg; ibuprofen 200 mg
Allegra D 12-Hour Tablets	Fexofenadine 60 mg; pseudoephedrine HCl 120 mg
Claritin-D 24 Hour Tablets	Loratadine 10 mg; pseudoephedrine sulfate 240 mg
Nasal Products	
Ayr Saline Nasal Gel	Sodium chloride; aloe; propylene glycol; glycerin
NasalCrom Spray	Cromolyn sodium 5.2 mg/spray
Ocean Spray	Sodium chloride 0.65%

Complementary Therapies

Ephedra (ma huang) and feverfew are commonly suggested herbal remedies for allergic rhinitis. Ephedra-containing products are banned by FDA owing to their serious adverse effects (e.g., stroke). Parthenolide, feverfew's biologically active component, may have anti-inflammatory properties, but its safety and efficacy in allergic rhinitis are unproved. (For further discussion of these types of products, see [Chapter 51](#).) Capsaicin-based nasal sprays (e.g., Sinus Buster) have shown promise in treating nonallergic rhinitis but not allergic rhinitis. Using local honey or homeopathic products containing known allergens (e.g., bioAllers Animal Hair and Dander Allergy Relief Liquid contains cat, cattle, dog, horse, and sheep wool extracts) to induce long-term resistance by repeated exposure to controlled amounts of allergen has not been proved to be safe or effective. Safety and efficacy data also are lacking for symptom-specific homeopathic remedies such as Sabadilla for nasal and ocular symptoms (red, watery eyes) and Wyethia for itching (See [Chapter 52](#) for a complete discussion of homeopathic products). The role of vitamin D in prevention and treatment

of allergic disorders is an emerging area of research.⁴⁹ Several small studies have shown patients with low dietary intake and low plasma vitamin D levels, especially in children, were more likely to have allergic rhinitis.⁴⁹ More research is needed on the role of vitamin D in the pathophysiology of allergies.

Assessment of Allergic Rhinitis: A Case-Based Approach

Asking the patient for a detailed description of signs and symptoms and obtaining the patient’s medical and medication use (previous and current) history are essential to determining whether the patient has allergic rhinitis or rhinitis related to other causes and is eligible for self-care ([Tables 11–11](#) and [11–12](#)).

The medical history may uncover other respiratory illnesses that complicate treatment of allergic rhinitis. The patient’s current medication list will alert the health care provider to possible interactions with nonprescription allergy medications. Any nonprescription products the patient has used to treat episodic allergic rhinitis, IAR, or PER should be identified, as well as whether they were effective and without adverse effects.

Case 11–2 presents an example of the assessment of a patient with allergic rhinitis.

Case 11–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient’s symptoms, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient complains of severe daytime fatigue and “runny nose” for the past 3 months.

Relevant Evaluation Criteria	Scenario/Model Outcome
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Symptoms started while patient was pregnant and she gave birth 3 weeks ago. Nothing seems to help.
c. Description of the patient's efforts to relieve the symptoms	Patient has tried Zicam nasal spray, Afrin nasal spray, and diphenhydramine.
d. Patient's identity	Elizabeth McKay
e. Patient's age, gender, height, and weight	36 years, female, 5 ft 7 in., 210 lb
f. Patient's occupation	Psychologist
g. Patient's dietary habits	Patient describes a well-balanced diet.
h. Patient's sleep habits	Patient reports disrupted sleep and probably only gets 4 hours per night.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Multivitamin 1 tablet every morning
j. Allergies	No known allergies
k. History of other adverse reactions to medications	None
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Allergic rhinitis commonly manifests as sneezing, itchy nose or eyes, and a "runny nose." Symptoms usually are worse in the morning and at night, with some relief during the day. Nonallergic rhinitis symptoms typically are present the entire day and do not include sneezing or itchy eyes and nose.
3. Identify exclusions for self-treatment (Figure 11-3).	Ms. McKay has symptoms of nonallergic rhinitis.
4. Formulate a comprehensive list of therapeutic alternatives for the	Options include

Relevant Evaluation Criteria	Scenario/Model Outcome
primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	(1) Refer patient to an appropriate health care provider. (2) Recommend self-care with a nonprescription antihistamine and nondrug measures. (3) Recommend self-care until patient can see an appropriate health care provider. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Ms. McKay should consult an appropriate health care provider.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"You should consult your primary care provider or other medical provider for treatment."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"This option is best, because your problem started when you were pregnant and has not resolved with various nonprescription products."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	n/a
Solicit follow-up questions from the patient or caregiver.	"Is this contagious?"
Answer the patient's or caregiver's questions.	"No. Your condition appears to be nonallergic rhinitis and may be due to anatomic changes in your nose

Relevant Evaluation Criteria	Scenario/Model Outcome
	related to your pregnancy.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Ms. McKay in 1–2 days to ensure that she sought medical care and made an appointment.

Key: n/a = Not applicable.

Patient Counseling for Allergic Rhinitis

The health care provider should emphasize that the best method of treating allergic rhinitis is to avoid allergens. Many patients, however, have no control over their work environment or are unable to implement all of the preventive measures at home. Such patients usually rely on allergy medications for symptom control. Patient counseling should include information about proper use of recommended medication(s) and about possible adverse effects, drug–drug and drug–disease interactions, and other precautions and warnings. The health care provider also should be aware of duplication of therapy with prescription INCS. Patient counseling should especially emphasize signs and symptoms indicating that the disorder has progressed to the point at which medical care is needed. The box “Patient Education for Allergic Rhinitis” presents specific information to provide in patient counseling.

Patient Education for Allergic Rhinitis

The primary objective of self-treatment is to prevent or reduce symptoms, which in turn will improve functioning and enhance the patient’s sense of

well-being. In some cases, prescription therapy such as a short course of oral corticosteroids may be needed to help control symptoms; other therapies and measures may be initiated when symptoms are especially severe. For most patients, carefully following instructions for nonprescription allergy medications and the self-care measures listed here will help ensure optimal therapeutic outcomes.

Nondrug Measures

- Avoidance of allergens is important regardless of whether allergy medications are being taken.
- For symptoms that develop mainly when the patient is outdoors:
 - Frequently check local pollen counts and air quality index.
 - Keep house and car windows shut; avoid yard work and outdoor sports on days with high levels of pollen (spring/summer), mold (late summer/fall), or pollution.
- For symptoms that occur mainly when the patient is indoors:
 - Try to remove the symptom trigger(s) (e.g., cats, house-dust mites, tobacco smoke, molds) from rooms.
 - Lower the humidity in the home to reduce molds. Use lower settings on humidifiers, repair damp basements and crawl spaces, vent kitchens and bathrooms, and remove houseplants.
 - Wash bedding in hot water (131°F [55°C]) every week, and encase mattresses and pillows in coverings resistant to house-dust mites.
- Nasal saline solutions may relieve nasal irritation and dryness, and aid in the removal of dried, encrusted, or thick mucus from the nose.

Nonprescription Medications

- Ask a health care provider for help in selecting an allergy medication that treats the most bothersome symptoms. If needed, additional medications can be added for other symptoms:
 - Intranasal steroids are effective for itchy eyes and noses,

sneezing, runny nose, and congestion.

- Antihistamines are effective for itching, sneezing, and runny nose but have little effect on nasal congestion.
 - Decongestants are effective for nasal congestion but have little effect on other symptoms.
 - Combination therapy with intranasal steroids, antihistamines, and decongestants is common.
 - Intranasal and ocular preparations are available to reduce nasal and eye symptoms, respectively.
 - Intranasal cromolyn is the preferred initial drug of choice during pregnancy and lactation. This medication is not absorbed into the body.
 - For intranasal products, follow the dosing and administration directions carefully. (See [Table 11–2.](#))
 - The most common adverse effects of nasal preparations include nasal stinging and burning.
- Allergy medications are more effective if they are used regularly rather than episodically:
 - If you have episodic or intermittent allergies, start allergy medications as soon as possible, before specific exposure to the allergen.
 - If you have persistent allergies, take allergy medications on a regular basis.

Nasal Congestion

- See the box “Patient Education for Colds” for information about relieving nasal congestion.

Rhinorrhea (Runny Nose) and Sneezing

- Many factors cause a “runny nose,” and depending on the causes, nonprescription steroids or antihistamines may only partially treat this symptom. Because some nonprescription antihistamines may make you very drowsy, the potential benefits of the medication must be weighed against the potential risks.

- Sneezing is a common and sometimes bothersome symptom. Sneezing may be reduced with nonprescription intranasal steroids or antihistamines. The potential benefits of using antihistamines must be weighed against the potential risks.
- Intranasal steroids and oral antihistamines are the preferred initial therapeutic agents for runny nose and sneezing in persons who are eligible for self-care (see exclusions in [Figure 11-3](#)).
- Note the following precautions for use of nonprescription intranasal corticosteroids:
 - Intranasal corticosteroids may irritate the nose or the bottle tip can injure the nose if it is used forcefully.
 - Follow the package labeling carefully and use the lowest dose for the shortest amount of time, especially in children.
 - If you have HIV infection/AIDS and are being treated with protease inhibitors, check with your primary care provider before using intranasal corticosteroids.

Antihistamines

- There are two types of antihistamines: sedating and nonsedating. Cetirizine, fexofenadine, levocetirizine, and loratadine are nonsedating antihistamines and usually do not cause significant drowsiness.
- Note the following adverse effects for antihistamines:
 - The sedating antihistamines cause drowsiness and impair mental alertness. Mental alertness is impaired even if you do not feel drowsy or if you took the dose the previous evening. While taking these medications, do not drive a vehicle, operate machinery, or engage in other activities that require alertness.
 - Sedating antihistamines may cause sensitivity to sunlight. Use sunscreens and wear protective clothing when outdoors.
 - Use of sedating antihistamines may cause dryness in your mouth, nose, and other areas of the body.
 - Children and older persons may experience unexpected and paradoxical excitement with sedating antihistamines.
 - Older patients should avoid sedating antihistamines and

may need lower doses of nonsedating antihistamines because they are more sensitive to the effects of these agents and more often take other medications that interact with these drugs.

- Do not use antihistamines:
 - If you are allergic to antihistamines or similar medications
 - If you are breastfeeding
- Do not give antihistamines to newborns or premature infants unless directed to do so by a qualified health care provider.
- Note the following precautions for use of nonprescription antihistamines:
 - Persons with glaucoma, stenosing peptic ulcer, symptomatic enlarged prostate, bladder neck obstruction, or stomach or intestinal blockage should not use sedating (first-generation) antihistamines.
 - Persons with lower respiratory tract disease (e.g., emphysema or chronic bronchitis) should be advised to use sedating antihistamines with caution.
 - Persons with esophageal narrowing, abnormal esophageal peristalsis, or problems swallowing tablets should not take the 12- or 24-hour sustained-release dosage forms of loratadine combined with pseudoephedrine. Esophageal obstruction and perforation have been reported with use of these sustained-release dosage forms.
- All antihistamines interact with the following drugs:
 - Alcohol, sedatives, opioid analgesics, and other central nervous system depressants may cause additive depressive effects when taken with antihistamines.
 - Anticholinergic drugs (e.g., ipratropium)
 - Potassium chloride, which may increase the risk of ulcer formation when taken with antihistamines
- Specific sedating antihistamines interact with certain drugs as follows:

- Chlorpheniramine may increase the adverse effects of phenytoin.
- Diphenhydramine may increase the adverse effects of metoprolol and brexpiprazole.
- Nonsedating antihistamines interact with specific drugs as follows:
 - Fexofenadine interacts with ketoconazole, erythromycin, and antacids. Also avoid taking with fruit juice.
 - Loratadine interacts with amiodarone.
- Store all medications according to the manufacturer's instructions.

When to Seek Medical Attention

- Seek medical attention in the following situations:
 - Your allergy symptoms worsen while you are taking nonprescription medications or do not decrease after 2–4 weeks of treatment.
 - You develop signs or symptoms of secondary bacterial infections (e.g., thick nasal or respiratory secretions that are not clear, oral temperature higher than 101.5°F [38.6°C], shortness of breath, chest congestion, wheezing, significant ear pain, rash).

Evaluation of Patient Outcomes for Allergic Rhinitis

Many patients achieve symptomatic relief with initial nonprescription drug therapy in 3–4 days, but complete relief of symptoms may take 2–4 weeks. After this time frame, a follow-up telephone call from the health care provider or a scheduled office appointment is recommended to determine whether symptom control has been achieved or if the patient is encountering any adverse effects or problems. A validated instrument such as the Rhinitis Control Assessment Test may be used to monitor response to therapy.⁵⁰

Patients who respond poorly to treatment should be assessed to determine whether they are practicing recommended allergen avoidance strategies and are adhering to medication regimens. Options for patients who do not achieve relief include increasing current medications to maximally effective dosages and changing to a different medication or dosage formulation. Patients who do not respond to nonprescription therapy should be referred back to their primary care providers for prescription medications such as intranasal antihistamines, systemic corticosteroids, leukotriene inhibitors, anticholinergics, or immunotherapy. In such cases, clinical reassessment also is indicated, and the diagnosis of allergic rhinitis may need to be reconsidered. Patients who demonstrate any of the warning signs or symptoms listed in the box “Patient Education for Allergic Rhinitis” should be referred to an appropriate health care provider.

Key Points for Disorders Related to Colds and Allergic Rhinitis

- Colds are self-limiting viral infections characterized by initial sore throat followed by nasal symptoms and nonproductive cough.
- Medical referral is appropriate for patients with suspected colds who are immunocompromised, have underlying cardiopulmonary diseases, or exhibit so-called alarm symptoms or signs (high fever, chest pain, shortness of breath, or wheezing).
- Treatment for colds is symptomatic and targeted at the most bothersome symptoms.
- Decongestants are the most common nonprescription agents for treatment for congestion related to colds and allergic rhinitis, but caution is advised with their use in patients with hypertension, diabetes, and other chronic diseases.
- The treatment approach to allergic rhinitis is sequential and consists of allergen avoidance, pharmacotherapy, and allergen immunotherapy.
- Medical referral is appropriate for patients with symptoms

suggestive of nonallergic rhinitis, otitis media, sinusitis, or lower respiratory tract problems such as pneumonia, asthma, or bronchitis, and for those patients who fail to respond to nonprescription medications.

- Antihistamines are commonly used to control allergic rhinitis symptoms. Nonsedating (second-generation) antihistamines are preferred over sedating (first-generation) antihistamines on the basis of safety and efficacy data.

Chapter 12: Cough

Authors: Karen J. Tietze

Cough is an important defensive respiratory reflex for airway protection. As a clinical problem, however, cough has potentially significant adverse physical and psychological consequences, as well as substantial economic impact. Cough is the most common symptom for which patients seek outpatient medical care.¹ It also is a common reason for emergency department visits. In 2015, cough was the second most common reason among children younger than 15 years for emergency department visits and the fourth most common reason for adult visits.² Americans spend more than \$8.6 billion annually on nonprescription cough and cold and related medications, more than for any other nonprescription sales category.³

Pathophysiology of Cough

Cough is initiated by stimulation of chemically and mechanically sensitive, vagally mediated bronchopulmonary and extrapulmonary sensory nerves in the pharynx, larynx, esophagus, and tracheobronchial airway epithelium.⁴ The number of afferent nerves activated and the intensity of activation may influence the cough threshold. Receptors in the larynx, trachea, and proximal large airways are more sensitive to mechanical stimulation, whereas distal airway receptors are more sensitive to chemical stimulation.⁵ A complex medullary brainstem network (“cough control center”) processes the sensory input and stimulates the motor efferents. Voluntary cough is controlled by the cerebral cortex.⁵ In viral infections, cough is mediated by a different, though not well understood, mechanism.⁶ The term *cough hypersensitivity syndrome* describes the proposed neural dysregulation resulting in cough associated with some chronic medical conditions.⁷

A cough starts with a deep inspiration, followed by closure of the glottis and forceful contraction of the chest wall, abdominal wall, and diaphragmatic muscles against the closed glottis; pressure within the thoracic cavity may reach 300 mm Hg.⁸ With reopening of the glottis, air is expelled with a velocity of approximately 11–15 m/second, propelling mucus, cellular debris, and foreign material out of the respiratory system.⁹ Cough may occur in epochs (“coughing

fits”).

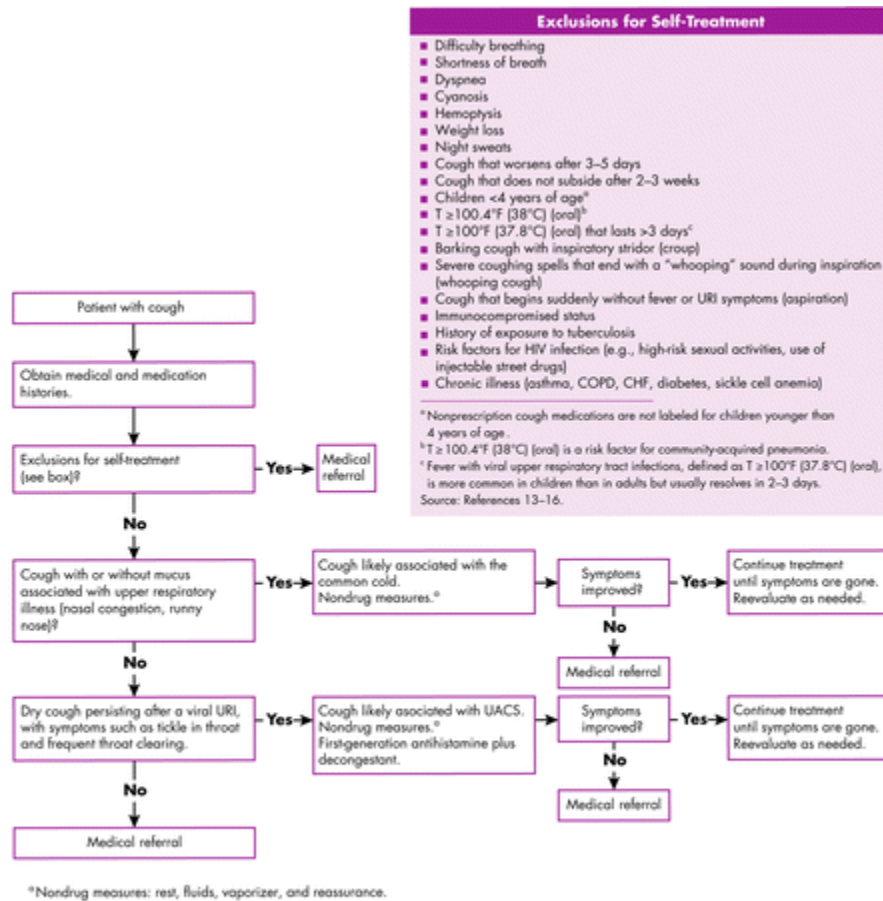
Cough, classified as *acute* (duration of less than 3 weeks), *subacute* (duration of 3–8 weeks), or *chronic* (duration of more than 8 weeks), is a symptom of diverse infectious and noninfectious disorders ([Table 12-1](#)).^{10,11} In children, cough also may be a symptom of aspiration caused by poor coordination of sucking and swallowing or esophageal motility disorders. Angiotensin-converting enzyme inhibitors cause dry cough in approximately 13.5% of persons taking these medications, with a higher rate of cough (28%) for patients with heart failure.¹² Systemic and ophthalmic beta-adrenergic blockers may cause cough in patients with obstructive airway diseases such as asthma and chronic obstructive pulmonary disease (COPD).

Clinical Presentation of Cough

Coughs are described as productive or nonproductive. A *productive* cough (a wet or “chesty” cough) serves a useful physiologic purpose: evacuation of secretions from the lower respiratory tract that, if retained, could impair ventilation and the lungs’ ability to resist infection. Productive coughs may be effective, with easily expelled secretions, or ineffective to a variable degree, with secretions that are difficult to expel. The appearance of the expectorated secretions is not always a reliable diagnostic indicator, but this material typically is clear with bronchitis and purulent with bacterial infection. Anaerobic bacterial infections are associated with a distinct putrid malodor. *Nonproductive* cough (dry or “hacking” cough), which may be associated with viral and atypical bacterial infections, gastroesophageal reflux disease (GERD), cardiac disease, and some medications, serves no useful physiologic purpose.

Common complications of cough include exhaustion, sleep deprivation, musculoskeletal pain, hoarseness, excessive perspiration, social embarrassment, and urinary incontinence. Less common complications include cardiac dysrhythmias, syncope, stroke, pneumothorax, and rib fractures. Mechanical irritation from coughing may cause sore throat. Cough may lead to prolonged absence from work or school, withdrawal from social activities, and anxiety from fear that the cough is a symptom of a serious illness, such as cancer or tuberculosis.

Algorithm: Cough



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Figure 12–1 Self-care for cough. Key: CHF = Congestive heart failure; COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus; T = temperature; UACS = upper airway cough syndrome; URI = upper respiratory infection.

Treatment of Cough

Treatment Goals

The primary goal of self-treatment for cough is to reduce the number and severity of coughing episodes. The secondary goal is to prevent complications.

Treatment is symptomatic. Recognition of the underlying disorder or condition—the basis for the cough—is required for effective and definitive management.

General Treatment Approach

Selection of a medication for self-care for cough depends on the nature and underlying cause of the cough. [Figure 12–1](#) lists exclusions for self-care.^{13–16} These exclusions are based on the presence of signs and symptoms of potentially serious medical conditions associated with cough that require further evaluation. *Antitussives* (cough suppressants) control or eliminate cough and are the drugs of choice for treatment of nonproductive cough. Antitussives should not be used to treat productive cough unless the potential benefit outweighs the risk (as with significant nocturnal cough). Suppression of productive coughs may lead to retention of lower respiratory tract secretions, increasing the risk of airway obstruction and secondary bacterial infection. *Protussives* (expectorants) change the consistency of mucus and increase the volume of expectorated sputum and may provide some relief for patients in whom coughing expels thick, tenacious secretions from the lungs with difficulty.

Table 12–1 Common Causes of Cough

Classification	Etiologic Contributors
Acute	Viral URTI (common cold), acute bacterial sinusitis, acute bronchitis, pertussis, allergic rhinitis, COPD exacerbations, pneumonia, environmental irritants
Subacute	Postinfectious (e.g., <i>Mycoplasma pneumoniae</i> , <i>Bordetella pertussis</i>), congestive heart failure with fluid overload
Chronic	UACS, asthma or asthma-like conditions, GERD, COPD, chronic bronchitis

Key: COPD = Chronic obstructive pulmonary disease; GERD = gastroesophageal reflux disease; UACS = upper airway cough syndrome; URTI = upper respiratory tract infection.

Source: [References 10](#) and [11](#).

Cough medications are marketed in a variety of dosage forms—syrups, liquids, solutions, suspensions, tablets, capsules, liquid gels, lozenges, oral granules, oral strips, topical ointments and creams, topical patches, and vaporizer solutions. Generic formulations are widely available. The U.S. Food and Drug Administration (FDA) permits various combinations of antitussives, protussives, analgesics, decongestants, and antihistamines. Of note, however, combinations of antitussives and protussives are potentially counterproductive. Unnecessary active ingredients contribute to increased risk for avoidable adverse effects and drug interactions.

Nonpharmacologic Therapy

Nonpharmacologic therapy includes use of nonmedicated lozenges and hard candies, humidification, interventions to promote nasal drainage, and hydration. Nonmedicated lozenges and hard candies may reduce cough by stimulating production of saliva, thereby decreasing throat irritation. Humidifiers (ultrasonic, impeller, and evaporative) increase the amount of moisture in inspired air, which may soothe irritated airways. However, high humidity may increase environmental mold, dust mites, white dust from minerals released into the air, and microorganisms. Vaporizers (humidifiers with a medication well or cup for volatile inhalants) produce a medicated vapor. Cool-mist humidifiers and vaporizers are preferred because fewer bacteria grow at the cooler temperatures and the risk of scalding with use of a hot water–based device is eliminated. Humidifiers and vaporizers require daily cleaning and weekly disinfection.

Babies and young children up to approximately 2 years of age cannot blow their noses; a rubber bulb nasal syringe may be used to clear the nasal passages and reduce cough caused by postnasal drip. Propping infants upright when they sleep and raising the head of the bed at night will promote drainage of nasal secretions.

Maintaining adequate hydration promotes formation of less viscous secretions that are easier to expel. Caution is warranted, however, with measures to increase hydration in patients with lower respiratory tract infections, heart failure, renal failure, or other medical conditions potentially exacerbated by overhydration.

Pharmacologic Therapy

Table 12–2 lists examples of antitussive and expectorant products.

Oral Antitussives

FDA-approved nonprescription oral antitussives include codeine (codeine, codeine phosphate, codeine sulfate), dextromethorphan (dextromethorphan, dextromethorphan hydrobromide), diphenhydramine (diphenhydramine citrate, diphenhydramine hydrochloride), and chlorpheniramine hydrochloride.¹⁷ Nonprescription oral antitussives typically are used as needed within the limits of the maximum recommended daily dose. Nonprescription topical antitussives also are typically used on an as-needed basis, not to exceed the maximum recommended daily dose.

Codeine

At antitussive dosages, codeine is a Schedule V narcotic available without a prescription in some states. Codeine-containing Schedule C–V products must contain no more than 200 mg of codeine per 100 milliliters.¹⁸

Codeine acts centrally on the medulla to increase the cough threshold. Codeine is methylmorphine; one or more metabolites (morphine, norcodone, and others) may be the active antitussive. Codeine is well absorbed orally, with a 15- to 30-minute time to onset of action and a 4- to 6-hour duration of effect. The elimination half-life is 2.5–3 hours. Ten percent of a codeine dose is demethylated in the liver to form morphine; approximately 3%–16% of the drug is eliminated unchanged in the urine. The complicated metabolic pathway includes cytochrome P450 (CYP) 2D6, CYP3A4, and uridine 5'-diphospho-glucuronosyltransferase (UGT) 2B7. CYP2D6 polymorphisms lead to unpredictable clinical response and potential toxicity in affected persons. Poor metabolizers may not benefit from codeine. Extensive metabolizers are at increased risk for sedation and respiratory depression.

Codeine is indicated for the suppression of nonproductive cough caused by chemical or mechanical respiratory tract irritation. In 2018, FDA limited the use of prescription opioid cough and cold medicines to adults 18 years and older.¹⁹ FDA did not address nonprescription codeine product labeling. Table 12–3 lists FDA-approved dosages for codeine and other nonprescription cough products.

Reduced doses are appropriate for patients of advanced age and the debilitated. Codeine is available as oral solutions, liquids, suspensions, and syrups in combination with other active ingredients, including guaifenesin, antihistamines, and decongestants. Alcohol-, dye-, gluten-, and sucrose-free formulations also are available.

Usual antitussive codeine dosages are associated with low toxicity and little risk of addiction. The most common adverse effects associated with antitussive codeine dosages are nausea, vomiting, sedation, dizziness, and constipation. The black box warning for codeine includes the risk of serious, life-threatening, or fatal respiratory depression and the risk of opioid addiction, abuse, and misuse. Codeine syrup containing the antihistamine promethazine hydrochloride, when mixed with soft drinks and/or alcohol and sometimes candy (common street names include “purple drank,” “sizzurp,” “syrup,” and “lean”), is abused for the sedative effect. The lethal dose of codeine in adults is 0.5–1 g, with death from marked respiratory depression and cardiopulmonary collapse. Concomitant use of codeine and central nervous system (CNS) depressants causes additive CNS depression. Strong CYP2D6 inhibitors may block the conversion of codeine to the active metabolites. [Table 12–4](#) lists clinically important codeine–drug interactions.²⁰ Codeine is contraindicated in patients with known codeine hypersensitivity and during labor when a premature birth is anticipated. Patients with impaired respiratory reserve (as in asthma or COPD) or preexisting respiratory depression, drug addicts, and persons who take other respiratory depressants or sedatives, including alcohol, should use codeine with caution.

Table 12-2 Selected Nonprescription Products for Cough	
Trade Name	Primary Ingredient(s)
Single-Ingredient Products	
Delsym, Robitussin Nighttime Cough DM, Hold DM, Robafen DM	Dextromethorphan
Robafen, Mucinex for Kids, Tussin	Guaifenesin
Vicks VapoDrops, Halls Mentho-Lyptus Drops	Menthol
Combination Products	
Vicks VapoRub, Mentholatum	Camphor/menthol/

Trade Name	Primary Ingredient(s)
	eucalyptus oil
Chlo Tuss EX	Chlophedianol/ guaifenesin
Guaiatussin AC, Virtussin A/C, Cheratussin AC	Codeine/guaifenesin
Mucinex-DM, Cheracol D, Vicks 44E, Robitussin Cough & Chest Congestion DM, Triaminic Cough and Cold Congestion	Dextromethorphan/ guaifenesin
Benylin Chesty Coughs	Diphenhydramine/ levomenthol

Dextromethorphan

Dextromethorphan is a nonopioid with no analgesic, sedative, respiratory depressant, or addictive properties at usual antitussive doses.

Dextromethorphan, the methylated dextrorotatory analogue of levorphanol (itself a codeine analogue), acts centrally in the medulla to increase the cough threshold. It is well absorbed orally, with a 15- to 30-minute time to onset of action and a 3- to 6-hour duration of effect. Dextromethorphan undergoes polymorphic metabolism, with a usual elimination half-life of 1.2–2.2 hours. However, the half-life may be as long as 45 hours in people with a poor metabolism phenotype.

Dextromethorphan is indicated for the suppression of nonproductive cough caused by chemical or mechanical respiratory tract irritation. The efficacy and safety of dextromethorphan as an antitussive drug in children have not been established.²¹ **Table 12–3** lists FDA-approved dextromethorphan dosages.

Table 12–3 Dosage Guidelines for Nonprescription Oral Antitussives and Expectorants

Drug	Dosage (maximum daily dose)		
	Adults/Children ≥12 Years	Children 6 to <12 Years	Children 2 to <6 Years ^a
Chlophedianol ^{b,c}	25 mg every 6–8 hours PRN (100 mg)	12.5 mg every 6–8 hours PRN (50 mg)	12.5 mg every 6–8 hours PRN (50 mg)
Codeine ^d	Adults 18 years of age and	Contraindicated	Contraindicated

Drug	Dosage (maximum daily dose)		
	Adults/Children ≥12 Years	Children 6 to <12 Years	Children 2 to <6 Years ^a
	older: 10–20 mg every 4–6 hours PRN (120 mg)		
Dextromethorphan hydrobromide ^b	10–20 mg every 4 hours or 30 mg every 6–8 hours PRN (120 mg)	5–10 mg every 4 hours or 15 mg every 6–8 hours PRN (60 mg)	2.5–5 mg every 4 hours or 7.5 mg every 6–8 hours PRN (30 mg)
Diphenhydramine citrate ^{b,c}	38 mg every 4 hours PRN (228 mg)	19 mg every 4 hours PRN (114 mg)	9.5 mg every 4 hours PRN (57 mg)
Diphenhydramine HCl ^{b,c}	25 mg every 4 hours PRN (150 mg)	12.5 mg every 4 hours PRN (75 mg)	6.25 mg every 4 hours PRN (37.5 mg)
Guaifenesin ^b	200–400 mg every 4 hours PRN (2.4 g)	100–200 mg every 4 hours PRN (1.2 g)	50–100 mg every 4 hours PRN (600 mg)

^a The Consumer Health Care Products Association announced in October 2008 that manufacturers were voluntarily updating cough and cold product labels to state “do not use” in children younger than 4 years.⁴⁵ These actions have not changed the official monograph for cold, cough, allergy, bronchodilator, and antiasthmatic drug products.¹⁷

^b Not recommended for use in children younger than 2 years; no FDA-approved dosing recommendations.

^c FDA recommends that the labels on nonprescription products not provide dosage information for children younger than 6 years.

^d Prescription cough and cold medications containing codeine or hydrocodone are contraindicated in children younger than 18 years of age.¹⁹

Key: CFR = *Code of Federal Regulations*; FDA = U.S. Food and Drug Administration; PRN = as needed.

Source: [Reference 17](#).

Table 12–4 Clinically Important Drug–Drug Interactions With Nonprescription Antitussive Agents^a

Antitussive	Drug/Drug Class	Potential Interaction	Management/Preventive Measure(s)
Codeine	Alvimopan	Opioid use increases the risk of alvimopan adverse reactions.	Discontinue opioids at least 7 days before initiating alvimopan.
Codeine	CNS depressants, including alcohol, benzodiazepines, sedating antihistamines, antipsychotics, antianxiety agents, cannabidiol	CNS depressants enhance the CNS depressant effect of codeine.	Avoid concurrent use if possible.
Codeine	Strong CYP2D6 inhibitors (e.g., bupropion, fluoxetine, paroxetine, quinidine, gerbinafine, dacomitinib)	Strong CYP2D6 inhibitors may block the metabolism of codeine to the active metabolites leading to a reduced effect.	Avoid concurrent use if possible.
Codeine	Strong CYP3A4 inducers (e.g., rifampin, phenytoin)	Strong CYP3A4 inducers may increase the metabolism of codeine to inactive metabolites, leading to a reduced effect.	Avoid concurrent use if possible.
Codeine	Eluxadoline	Codeine may enhance eluxadoline-associated constipation.	Avoid concurrent use if possible.
Codeine	Mixed agonist/antagonist opioids (e.g., buprenorphine)	Mixed agonist/antagonists may reduce the therapeutic effect of codeine.	Avoid concurrent use if possible.
Codeine	Naltrexone	Naltrexone may reduce the therapeutic effect of codeine.	Avoid concurrent use if possible.

Dextromethorphan	Strong CYP2D6 inhibitors (e.g., bupropion, fluoxetine, paroxetine, quinidine, terbinafine, dacomitinib)	Strong CYP2D6 inhibitors may decrease dextromethorphan metabolism, increasing the psychoactive effects of dextromethorphan.	Avoid concurrent use if possible.
Dextromethorphan	Serotonin reuptake inhibitors (e.g., citalopram, escitalopram, fluoxetine, sertraline, vilazodone)	Serotonin modulators may increase the risk of serotonergic (psychoactive) effects of dextromethorphan.	Avoid concurrent use if possible.
Dextromethorphan	MAO inhibitors, including rasagiline, selegiline, isocarboxazid, phenelzine, and tranylcypromine	MAO inhibitors may increase dextromethorphan-associated serotonergic adverse effects.	Avoid concurrent use if possible.

^a See [Chapter 11](#) (Table 11–6) for diphenhydramine–drug interactions.

Key: CNS = Central nervous system; CYP = cytochrome P450; MAO = monoamine oxidase.

Source: [Reference 20](#).

Dextromethorphan, as a single ingredient and in combination with active ingredients such as guaifenesin, acetaminophen, antihistamines, and decongestants, is marketed in the form of syrups, liquids, solutions, extended-release oral suspensions, elixirs, drops, gels, liquid-filled gel caps, tablets, capsules, powders, granules, strips, and lozenges. Alcohol-, sucrose-, gluten-, and dye-free formulations are available.

Dextromethorphan has a wide margin of safety. Adverse effects with usual doses are uncommon but may include drowsiness, nausea or vomiting, stomach discomfort, or constipation. Dextromethorphan overdoses cause confusion, excitation, nervousness, irritability, restlessness, and drowsiness, as well as severe nausea and vomiting; respiratory depression may occur with very high doses. Additive CNS depression occurs with alcohol, antihistamines, and psychotropic medications. The combination of monoamine oxidase

inhibitors (MAOIs) and dextromethorphan may cause *serotonergic syndrome* (manifested as increased blood pressure, hyperpyrexia, arrhythmias, and myoclonus). Dextromethorphan should not be taken for at least 14 days after the MAOI is discontinued. [Table 12–4](#) lists clinically important dextromethorphan–drug interactions. Patients who have known hypersensitivity to dextromethorphan or who have a previous history of dextromethorphan dependence should not take this drug.

Dextromethorphan is abused for its phencyclidine-like euphoric effect (“robotripping”).²² At least 17 states limit the sale of nonprescription cough medicine containing dextromethorphan to adults 18 years of age and older.²³ The usual requirement for sale is proof of age. Four progressive dose-related plateaus starting with doses as low as 1.5 mg/kg are described.²⁴ Each plateau is characterized by euphoric manifestations, ranging from mild stimulation and alcohol-like intoxication to dissociative hallucinations. Abuse of dextromethorphan may be associated with psychosis and mania; such abuse is especially common among male adolescents.²⁵

Diphenhydramine

Diphenhydramine, a nonselective (first-generation) antihistamine with significant sedating and anticholinergic properties, acts centrally in the medulla to raise the cough threshold. Second-generation antihistamines (e.g., loratadine, fexofenadine) lack antitussive activity. Diphenhydramine is well absorbed after oral administration, with a bioavailability of 40%–70%, a time to onset of action of approximately 15 minutes, and a duration of action of approximately 4–6 hours. The volume of distribution is 3.3–4.5 L/kg. Approximately one half of a dose of diphenhydramine is hepatically metabolized to *N*-demethyl, acetyl, and methoxyacetic acid, with a clearance rate of 0.4–0.7 L/kg per hour; the remainder is excreted unchanged in the urine.

Diphenhydramine is indicated for the suppression of nonproductive cough caused by chemical or mechanical respiratory tract irritation. [Table 12–3](#) lists FDA-approved diphenhydramine dosages. A common ingredient in cold and allergy products, diphenhydramine is available in multiple dosage formulations, including an alcohol-free syrup specifically indicated for cough. Signs and symptoms of diphenhydramine overdose include mild to severe CNS depression (e.g., mental confusion, sedation, respiratory depression),

hypotension, and CNS stimulation (e.g., hallucinations, convulsions).

Adverse effects of diphenhydramine include drowsiness, disturbed coordination, respiratory depression, blurred vision, urinary retention, dry mouth, and dry respiratory secretions. Uncommon adverse effects reported with use of this drug include acute dystonic reactions such as oculogyric crisis (sustained upturning of the eyeballs), torticollis (involuntary intermittent or sustained neck muscle contraction, often with a head tilt), and catatonia-like states, as well as allergic and photoallergic reactions. Diphenhydramine may cause excitability, especially in children. It also potentiates the depressant effects of narcotics, nonnarcotic analgesics, benzodiazepines, tranquilizers, and alcohol on the CNS, and it intensifies the anticholinergic effect of MAOIs and other anticholinergics. (See Table 11–6 in [Chapter 11](#) for clinically important diphenhydramine–drug interactions.) Diphenhydramine is contraindicated in patients with known hypersensitivity to diphenhydramine or structurally similar antihistamines. Diphenhydramine should be used with caution in patients with diseases or conditions potentially exacerbated by drugs with anticholinergic activity, including narrow-angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy, bladder neck obstruction, asthma and other lower respiratory tract disease, elevated intraocular pressure, hyperthyroidism, cardiovascular disease, and hypertension. Because of the associated increased risk of toxicity, diphenhydramine-containing antitussives should not be used with any other diphenhydramine-containing product, including topical products.

Chlophedianol

Chlophedianol is a centrally acting oral antitussive originally marketed in 1960 as a prescription drug. Reintroduced as a nonprescription product in late 2009, chlophedianol is an alkylamine antihistamine derivative with antitussive, moderate local anesthetic, and mild anticholinergic effects. Chlophedianol is indicated for the suppression of nonproductive cough caused by chemical or mechanical respiratory tract irritation. [Table 12–3](#) lists the FDA-approved chlophedianol dosages. Chlophedianol is marketed in combination with guaifenesin, antihistamines, and/or decongestants in the form of oral liquids, syrups, and tablets. Sugar-, alcohol-, dye-, and gluten-free products are available.

Published data for chlophedianol are limited. Its time to onset of maximal

effect is longer than that for codeine (4 hours versus 30 minutes), in addition to a longer duration of action.²⁶ Chlophedianol is metabolized hepatically and eliminated renally. Adverse effects include excitation, hyperirritability, nightmares, hallucinations, hypersensitivity, and urticaria. Dry mouth, vertigo, visual disturbances, nausea, vomiting, and drowsiness have been associated with large doses. Chlophedianol–drug interactions have not been evaluated. Chlophedianol is contraindicated in patients with known chlophedianol hypersensitivity.

Protussives (Expectorants)

Guaifenesin (glyceryl guaiacolate), the only FDA-approved expectorant, is indicated for the symptomatic relief of acute, ineffective productive cough.¹⁷ Guaifenesin is not indicated for chronic cough associated with chronic lower respiratory tract diseases such as asthma, COPD, or emphysema, or for smoker's cough. Guaifenesin purportedly loosens and thins lower respiratory tract secretions, making minimally productive coughs more productive. Recent randomized, placebo-controlled trials in adults with cough associated with respiratory tract infections failed to demonstrate significant effects on sputum biophysical properties.^{27,28} Although its pharmacokinetic properties are not well described, guaifenesin appears to be well absorbed after oral administration, with a half-life of approximately 1 hour.

Table 12–3 lists FDA-approved dosages of guaifenesin. Guaifenesin is marketed as oral liquids, syrups, solutions, granules, and immediate-release and extended-release tablets. Alcohol-, sucrose-, and dye-free formulations also are available. Most reports of guaifenesin overdose involve combinations of drugs and therefore are difficult to assess. However, signs and symptoms of overdose appear to be extensions of the adverse effects.

Guaifenesin generally is well tolerated. Adverse effects include nausea, vomiting, dizziness, headache, rash, diarrhea, drowsiness, and stomach pain. Large doses of this agent, either alone or in combination with ephedrine or pseudoephedrine, have been associated with development of renal calculi.²⁹ No guaifenesin–drug interactions have been reported. Guaifenesin is contraindicated in patients with a known hypersensitivity to guaifenesin.

Topical Antitussives

Camphor and menthol are the only FDA-approved topical antitussives.¹⁷ Other volatile oils (e.g., eucalyptus), common in many cough and cold preparations, impart a strong medicinal odor to products but are not FDA-approved antitussives. At subtherapeutic doses, menthol is a common flavoring agent. Although the mechanism of action is not well described, inhaled camphor and menthol vapors stimulate afferent sensory neuron “cold and menthol receptors” (TRPM8) within the nose and mucosa, creating a local anesthetic sensation and a sense of improved airflow; cough reflex sensitivity may be suppressed with these agents.³⁰ However, objective evidence of antitussive efficacy is very limited. Skin, nose, or eye burning sensations and/or irritation may occur with topical application. A possible drug interaction between menthol cough drops and warfarin resulting in reduced warfarin response has been reported.³¹ Table 12–5 provides administration guidelines for these agents.

Camphor- and menthol-containing ointments, creams, and solutions may splatter and cause serious burns if used near an open flame or placed in hot water or in a microwave oven. Camphor and menthol vapors may be ciliotoxic and proinflammatory throughout the upper and lower airways, especially in young children.³² These products also are toxic if ingested. Toxic effects include burning sensations in the mouth, nausea and vomiting, epigastric distress, restlessness, excitation, delirium, seizures, and death. Lethal oral doses in adults, children, and infants are approximately 4 grams, 0.5–1 gram, and 70 mg/kg, respectively.³³

Table 12–5 Administration Guidelines for Nonprescription Topical Antitussives (Adults and Children ≥2 Years^a)

Formulation	Administration
Ointments ^b	Apply a thick layer and rub on the throat and chest; application may be repeated PRN up to 3 times daily or as directed by primary care provider; loosen clothing around throat and chest so vapors reach the nose and mouth; cover with a warm, dry cloth (optional). Do not use in the nostrils, under the nose, by the mouth, on damaged skin, or with tight bandages.
Lozenges ^c	Allow lozenge to dissolve slowly in mouth; repeat hourly or as needed or as directed by a primary care provider.
Inhalation ^d	For products intended to be added directly to cold water for use in a steam vaporizer: Add measured solution to cold water; place the mixture in the vaporizer;

	breathe in the medicated vapors up to 3 times daily PRN.
	For products to be placed in the medication chamber of a hot steam vaporizer: Add water to vaporizer; place solution in medication chamber; breathe in the medicated vapors up to 3 times daily PRN.

^a For children younger than 2 years of age, consult a primary care provider.

^b Camphor 4.7%–5.3%; menthol 2.6%–2.8%.

^c Menthol lozenges, available in 5- or 10-mg formulation.

^d Camphor 6.2%; menthol 3.2%.

Key: PRN = As needed.

Source: [Reference 17](#).

Product Selection Guidelines

Efficacy

Although antitussives and expectorants have been marketed for decades, efficacy has been difficult to prove and may depend on the underlying cause of the cough. No good evidence is available to show that dextromethorphan, codeine, diphenhydramine, and guaifenesin are effective for treatment of acute cough in either adults or children^{34,35}; even less evidence is available for the efficacy of menthol, camphor, and chlophedianol.³⁶ Also lacking is evidence for or against the efficacy of nonprescription antitussives as adjuncts to antibiotics for the treatment of acute pneumonia.³⁷ Factors such as taste, smell, color, viscosity, sugar content, and personal expectation may contribute to a large placebo response (up to 85%).³⁸ Proof of efficacy will require data from well-designed trials in subjects with natural disease who are assessed with standardized objective outcome parameters. The American College of Chest Physicians (ACCP) publishes a series of evidence-based condition-specific cough guidelines.³⁹ With certain medical conditions, appropriate referral and assessment are required before initiation of nonprescription drug therapy.

Recommendations for the management of cough associated with specific

medical conditions include

- *Acute cough associated with the common cold:* Nondrug therapy is recommended for the generally benign and self-limiting cough associated with the common ⁴⁰ Antitussives, expectorants, antihistamines, and nonsteroidal anti-inflammatory drugs are ineffective.⁴¹
- *Postinfectious cough:* Nondrug therapy is recommended for management of subacute cough following an acute viral upper respiratory tract infection (“postinfectious cough”).⁴¹ An empiric trial of a first-generation antihistamine plus decongestant followed by a centrally acting antitussive (codeine or dextromethorphan) may be considered for cough persisting after a viral upper respiratory tract infection, but medical referral and assessment are required before initiation of such therapy.⁴¹ If necessary, codeine or dextromethorphan may be considered for postinfectious cough not due to bacterial sinusitis or *Bordetella pertussis* infection.⁴²
- *Upper airway cough syndrome (UACS):* In this syndrome, cough is caused by a variety of allergic and nonallergic conditions associated with upper airway irritation or inflammation, including postnasal drip (PND). Management is directed at eliminating the cause rather than controlling the cough. Following medical referral, empiric treatment of nonallergic UACS may include a first-generation antihistamine with or without an oral decongestant.⁴³
- *Cough associated with lower respiratory tract infection:* Provider assessment is needed before antitussives can be recommended for coughs associated with lower respiratory tract infections. The potential benefits from cough suppression (e.g., improved sleep) with centrally acting antitussives such as dextromethorphan or codeine may outweigh the potential risks (e.g., respiratory depression, retained secretions).

Dosage Formulations

Cough products are marketed in a variety of dosage formulations. Efficacy appears to be the same for all dosage formulations; patients may select a specific product on the basis of preference and convenience. Most products are formulated for dosage intervals of 4–6 hours, but some liquid and tablet dosage forms are specifically formulated for an extended dosage interval. For

example, some dextromethorphan products are formulated with polymer complexes (e.g., sulfonated styrene–divinylbenzene copolymer), conferring an extended dosage interval (8–12 hours). Patients self-treating nocturnal cough may prefer a product with this advantage.

Special Populations

In January 2008, FDA issued a public health advisory recommending that because of the risk of serious side effects, nonprescription cough and cold medicines should not be used in infants and children younger than 2 years.⁴⁴ In October 2008, the Consumer Healthcare Products Association (CHPA) announced that manufacturers were voluntarily updating cough and cold product labels to state “do not use” in children younger than 4 years.⁴⁵ To address the issue of inaccurate dosing, FDA released guidelines in May 2011 for liquid nonprescription drug products that include any type of dispensing device (dropper, cup, syringe, or spoon).⁴⁶ These products include liquid analgesics, liquid cough and cold products, and lactase replacement drops. The key points of the guidance are recommendations that

- A dosing device be included with all oral liquid nonprescription products
- The device be calibrated to the dose recommended in the product directions
- The device be used only with the product in which it is packaged
- The markings remain visible even when the liquid is in the device

Codeine’s efficacy and safety as an antitussive drug in children are not established. In 2018, FDA limited the use of prescription opioid cough and cold medicines to adults 18 years and older.¹⁹ FDA did not address nonprescription codeine product labeling.

An increased risk of congenital birth defects has been recognized with use of codeine during the first trimester of pregnancy. Codeine should be used during pregnancy only if the potential benefits outweigh the risks.

Nonteratogenic concerns include the risk of neonatal respiratory depression if codeine is taken close to the time of delivery and neonatal withdrawal if codeine is used regularly during the pregnancy. Codeine is excreted in breast milk and is associated with drowsiness in nursing infants.⁴⁷ (See the Preface for a detailed explanation of the pregnancy data.) Because older adults may be more susceptible to the sedating effects of codeine, dosing in this age group

should be started at the lower end of the recommended range and titrated as tolerated, with careful monitoring.

Dextromethorphan is viewed as probably safe for use during pregnancy.⁴⁸ It is not known whether dextromethorphan is excreted in breast milk. (See the Preface for a detailed explanation of the pregnancy data.) Because older adults may be more susceptible to the sedating effects of dextromethorphan, dosing in this age group, as with codeine, should be started at the lower end of the recommended range and titrated as tolerated, with careful monitoring.

Diphenhydramine is commonly used during pregnancy, although no controlled studies have been conducted in pregnant women. Diphenhydramine is excreted in breast milk and may cause unusual excitation and irritability in the infant; it may also decrease the flow of milk. (See the Preface for a detailed explanation of the pregnancy data.) Compared with the general population, elderly persons are more likely to experience dizziness, excessive sedation, syncope, confusion, and hypotension with diphenhydramine. The 2019 American Geriatrics Society Beers Criteria identify diphenhydramine, along with other nonprescription and prescription first-generation histamine-1 (H₁) receptor antihistamines, as potentially inappropriate medications in older adults.⁴⁹ Children and the elderly may experience paradoxical excitation, restlessness, and irritability with diphenhydramine. Dosing for the latter age group should be started at the lower end of the dosage range and titrated as tolerated, with careful monitoring.

Controlled studies on the use of guaifenesin or chlorpheniramine during pregnancy or breastfeeding are lacking. (See the Preface for a detailed explanation of the pregnancy data.) No special considerations have emerged regarding use of guaifenesin by older adults. Chlorpheniramine should be used with caution in sedated or debilitated patients.

Some cough formulations contain alcohol. Alcohol is a known teratogen and should be avoided during pregnancy.

Patient Factors

Cough is a symptom of many acute and chronic diseases ([Table 12–6](#)). Patients with identified exclusions for self-care

Table 12–6 Signs and Symptoms of Medical Conditions Associated With Cough

Disorder	Signs and Symptoms
Acute bronchitis ("chest cold")	Nonproductive cough initially but becomes productive; mucus initially clear (later becomes white, yellow or green); cough persisting for 1–3 weeks; mild dyspnea, mild wheezing; usually afebrile though may have a low-grade fever
Asthma	Wheezing or chest tightness; shortness of breath; nonproductive cough predominantly at night; cough in response to specific irritants such as dust, smoke, or pollen
Chronic bronchitis	Productive cough most days of the month at least 3 months of the year for at least 2 consecutive years
COPD	Persistent progressive dyspnea; chronic productive cough (may be intermittent or nonproductive)
GERD	Heartburn, regurgitation with sour taste in mouth; dysphagia, chest pain, chronic nonproductive cough; worsening symptoms with supine position
HF	Exertional dyspnea and shortness of breath; chronic nonproductive cough; fatigue; dependent edema
Lower respiratory tract infection UACS	Fever (mild to high); productive cough (thick, purulent, discolored mucus); shortness of breath
Viral URTI ("common cold")	Chronic nonproductive cough (persisting 8 weeks or longer) with sensation of mucus in throat
Acute bronchitis ("chest cold")	Acute sneezing, sore throat, nasal congestion; low-grade fever, nonproductive cough

Key: COPD = Chronic obstructive pulmonary disease; GERD = gastroesophageal reflux disease; HF = heart failure; UACS = upper airway cough syndrome; URTI = upper respiratory tract infection.

([Figure 12–1](#)) should be referred for further evaluation. Patients with known chronic diseases associated with cough, or with signs and symptoms suggestive of such diseases, should not attempt to self-treat cough, even if it is caused by an acute viral upper respiratory tract infection (URTI), because the acute infection may exacerbate the underlying disease. Patients with smoker's cough should be counseled regarding smoking cessation options; antitussives and expectorants are not indicated (see [Chapter 47](#)).

Dextromethorphan and diphenhydramine should not be taken concurrently with MAOIs. Diphenhydramine is highly sedating and should be avoided by patients for whom the anticholinergic properties of the drug present a risk of adverse effects or complications. First-generation antihistamines and decongestants should be used only if the potential benefit outweighs the risk (see [Chapter 11](#)).

Complementary Therapy

Hundreds of herbal and other complementary therapies are marketed for cough. However, available evidence does not support the use of complementary therapies for treating cough, and for some products, potential safety issues have been recognized. (See [Chapters 51](#) and [52](#), respectively, for information on such therapies.) For example, honey, a common but unproven home remedy,⁵⁰ should not be given to children younger than 1 year because of the risk of botulism from ingestion of honey contaminated with *Clostridium botulinum*.⁴⁰

Assessment of Cough: A Case-Based Approach

Before recommending any treatment, the health care provider needs to determine the duration of the cough (acute, subacute, or chronic), the nature of the cough (productive or nonproductive), and the presence of any associated signs or symptoms suggesting that the patient has an acute or chronic medical condition requiring referral ([Figure 12–1](#)). The health care provider's assessment also should review the patient's current prescription and nonprescription medications, medication allergies, and history of adverse drug reactions. In addition, the health care provider should ascertain how the

patient has treated the current cough, as well as previous coughs, and whether these treatments were satisfactory or effective.

Cases 12–1 and 12–2 provide examples of the assessment of two different patients with cough.

Case 12–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptoms(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient presented to her PCP 3 weeks ago with a several-day history of fever and gradually worsening pharyngitis, sore throat, hoarseness, and dry cough. Her PCP told her she had "walking pneumonia" and prescribed antibiotics. All of her symptoms have resolved except for a dry hacking cough. Today her PCP recommended she try a nonprescription cough medicine.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptoms	The cough bothers her at night.
c. Description of the patient's efforts to relieve the symptoms	The patient tried Halls honey-lemon cough drops and homemade horehound-peppermint cough drops without relief.
d. Patient's identity	Rebecca Wynter
e. Patient's age, gender, height, and weight	25 years, female, 5 ft 5 in., 125 lb
f. Patient's occupation	Elementary school teacher (second grade)

Relevant Evaluation Criteria	Scenario/Model Outcome
g. Patient's dietary habits	Cereal (with milk), whole grain breads, green salads, lean meats, fresh vegetables and fruit, low-fat yogurt
h. Patient's sleep habits	Sleeps 8-9 hours a night
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	The patient has a history of seizures currently treated with Dilantin (diphenylhydantoin). No routine nonprescription medications.
	No supplements.
j. Allergies	No known drug allergies
k. History of other adverse reactions to medications	None
l. Other (describe): _____	None
Assess	
2. Differentiate patient's signs/symptoms and correctly identify the patient's primary problems(s).	Rebecca is likely experiencing postinfectious subacute cough.
3. Identify exclusions for self-treatment.	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Take no action. (2) Recommend that the patient call her PCP for further assessment. (3) Recommend nondrug therapy (e.g., use a vaporizer at night). (4) Recommend self-care with a cough medication

Relevant Evaluation Criteria	Scenario/Model Outcome
	containing dextromethorphan or codeine.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Rebecca may treat her cough as needed with an antitussive containing dextromethorphan. The recommended dose for adults is dextromethorphan 10–20 mg every 4 hours as needed. Dextromethorphan is available in multiple dosage forms, including immediate- and extended-release tablets and capsules; lozenges; strips; and oral liquids, suspensions, and syrups. Single-entity products are preferred, to avoid potential side effects from unnecessary active ingredients.
6. Describe the recommended therapeutic approach to the patient or caregiver.	“Cough following pneumonia may be treated with a central-acting cough medication such as dextromethorphan or codeine. In our state, codeine-containing cough medications are available without a prescription. However, there is a known drug interaction between codeine and Dilantin resulting in reduced codeine effect. Avoid the combination if possible.”
	“Take dextromethorphan as needed for cough. Use an extended-release product before bedtime to help suppress cough throughout the night. Do not take more than the recommended dose for the specific product. Some medications may interact with dextromethorphan and some nonprescription medications (e.g., cold medications) may contain dextromethorphan. Ask your health care provider or PCP before starting any new medication.”
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	“Centrally active cough medications such as dextromethorphan and codeine may reduce post-pneumonia cough.”
Implement	
8. When recommending self-care with nonprescription	See the box “Patient Education for Cough.”

Relevant Evaluation Criteria	Scenario/Model Outcome
medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
Solicit follow-up questions from the patient or caregiver.	"Will dextromethorphan make me sleepy?"
Answer the patient's or caregiver's questions.	"Although dextromethorphan in usual doses is generally well tolerated, some people may experience dizziness, drowsiness, restlessness, nausea and vomiting, and stomach pain. Use caution when driving or performing tasks that require you to be awake and alert."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Ask Rebecca to call to update you on her response to treatment.

Key: PCP = Primary care provider.

Case 12-2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	

Relevant Evaluation Criteria	Scenario/Model Outcome
a. Description of symptoms(s) (i.e., nature, onset, duration, severity, associated symptoms)	A concerned spouse asks for something for her husband's cough. She states that his cough is worse than usual. He was diagnosed with COPD several years ago and did relatively well until about 6 months ago, when she noticed he was coughing more than usual. He coughs a lot, especially in the morning, when he brings up a large amount of clear mucus.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptoms.	The cough is worse in the mornings. His condition improved and his coughing was much less troublesome when he first started taking his COPD medications, but they do not seem to be working as well as they used to.
c. Description of the patient's efforts to relieve the symptoms	She states that her husband is very stoic. He has not told his pulmonologist about the worsening cough and has not tried any cough medications.
d. Patient's identity	Roger Marplewood
e. Patient's age, gender, height, and weight	56 years, male, 5 ft 10 in., 230 lb
f. Patient's occupation	Computer software engineer
g. Patient's dietary habits	Meat and potatoes; he does not like most fruits and vegetables.
h. Patient's sleep habits	Sleeps 10 hours a night
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	COPD diagnosed about 8 years ago. He currently takes Spiriva Respimat (tiotropium bromide) two inhalations once daily in the morning. He takes Motrin (ibuprofen) 2 tablets once or twice a week as needed for headaches. He does not take any dietary supplements.
j. Allergies	No known drug allergies
k. History of other adverse reactions to medications	None
l. Other (describe): _____	Used to smoke 2 packs a day but quit when he was diagnosed with COPD
Assess	

Relevant Evaluation Criteria	Scenario/Model Outcome
2. Differentiate patient's signs/symptoms and correctly identify the patient's primary problems(s).	Mr. Marplewood is likely experiencing worsening COPD symptoms.
3. Identify exclusions for self-treatment.	COPD
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Take no action. (2) Recommend that the patient see his primary care provider (PCP) or pulmonologist for further evaluation and treatment. (3) Recommend nondrug treatments (nonmedicated lozenges, take steamy baths/showers). (4) Recommend self-care with a nonprescription centrally acting antitussive or expectorant. (5) Recommend a combination of nondrug treatments, self-care with a nonprescription centrally acting antitussive or expectorant, and medical referral to his PCP or pulmonologist.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Refer Mr. Marplewood to his PCP or pulmonologist for further evaluation and management of his chronic cough. COPD is a progressive medical condition; changes in prescribed medication are common over time. Centrally acting antitussives may suppress respiration and therefore are not indicated for patients with COPD. The patient has a productive cough; expectorants are not indicated. Nondrug treatments are unlikely to reduce or resolve cough caused by COPD.
6. Describe the recommended therapeutic approach to	"Mr. Marplewood should consult with his pulmonologist about his worsening cough."

Relevant Evaluation Criteria	Scenario/Model Outcome
the patient or caregiver.	
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"It is common for patients with COPD to need to have their medications adjusted over time. Worsening cough may indicate that his COPD is getting worse and that his medications need to be reassessed."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	Criterion does not apply in this case.
Solicit follow-up questions from the patient or caregiver.	"Are there any supplements for COPD that might help with the cough?"
Answer the patient's or caregiver's questions.	"No. Some Internet sites state that COPD may be treated with supplements such as ginseng, turmeric, or fish oil, but there is no evidence for their effectiveness, and risks are recognized with use of each of these supplements."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Ask Mrs. Marplewood to let you know if she or her husband has any questions.

Patient Counseling for Cough

The health care provider should identify appropriate drugs and describe nondrug measures for treating the patient's type of cough. After a product is

recommended, the dosage guidelines, drug administration techniques (for topical drugs), and possible adverse effects, drug–drug interactions, and precautions or warnings should be fully explained. The health care provider should ensure that the patient understands when self-care for the cough is no longer adequate and that medical care must be sought. For patients with underlying medical disorders, the health care provider should identify which nonprescription medications are contraindicated, with specific reasons as appropriate, and what symptoms indicate the need to seek medical care. The box “Patient Education for Cough” lists specific information for patients.

Patient Education for Cough

The goals of self-treatment are (1) to reduce the number and severity of cough episodes and (2) to prevent complications. For most patients, carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

Nondrug Measures

- Stay well hydrated.
- Reduce throat irritation by slowly dissolving nonmedicated lozenges and candies in the mouth.
- Use humidifiers and vaporizers to increase the moisture in the air and possibly soothe irritated airways.
- Treat the underlying cause of cough (e.g., allergies).

Nonprescription Medications

- Cough is a symptom of an underlying disorder. Contact your primary care provider if you have any exclusions for self-care (listed in [Figure 12-1](#)).
- Select a product on the basis of the active ingredients and dosage formulation. Brand names frequently change and may not clearly represent the active ingredients.
- Slowly dissolve medicated lozenges in your mouth; do not chew.
- Swallow tablets and capsules whole; do not crush or chew.

- Follow the recommended dosing guidelines for each medication.
- Store all of these medications according to the manufacturer's recommendations. Do not use any expired drug.

Cough Suppressants (Antitussives)

- Cough suppressants control or eliminate cough and are the drugs of choice for treatment of nonproductive cough.
- Oral nonprescription cough suppressants include codeine (available without a prescription in some states), dextromethorphan, diphenhydramine, and chlorpheniramine.
- Topical nonprescription antitussives include camphor and menthol.
- Do not heat or microwave topical antitussives or add these preparations to hot water. Do not use topical antitussives near an open flame. Topical antitussive ointments and liquids are toxic if ingested.
- The most common adverse effects of codeine include nausea, vomiting, sedation, dizziness, and constipation.
- Dextromethorphan's adverse effects are uncommon but may include drowsiness, nausea, vomiting, stomach discomfort, and constipation.
- The most common diphenhydramine adverse effects include drowsiness, disturbed coordination, decreased respiration, blurred vision, difficult urination, and dry mouth.
- The most common chlorpheniramine adverse effects include nausea, dizziness, and drowsiness.
- Codeine, dextromethorphan, diphenhydramine, and chlorpheniramine interact with drugs that cause drowsiness (e.g., narcotics, sedatives, some antihistamines, alcohol).
- Dextromethorphan interacts with monoamine oxidase inhibitors (e.g., phenelzine, tranylcypromine, isocarboxazid). Do not take dextromethorphan within 14 days of taking one of these medications.
- Diphenhydramine and chlorpheniramine interact with drugs that have anticholinergic activity.
- Patients with impaired respiratory reserve (e.g., asthma, chronic obstructive pulmonary disease) should use codeine and

diphenhydramine with caution.

- Patients with narrow-angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy, bladder neck obstruction, elevated intraocular pressure, hyperthyroidism, heart disease, or hypertension should use diphenhydramine with caution.
- Talk with your primary care provider before using any medication while pregnant.
- Codeine and diphenhydramine are excreted in breast milk and may cause adverse effects in the child.
- Older adults and children may exhibit paradoxical excitation, restlessness, and irritability with use of diphenhydramine or chlorpheniramine. Older adults are more likely than the general population to experience adverse effects from diphenhydramine.

Expectorants (Protussives)

- Guaifenesin is the only available nonprescription protussive.
- Guaifenesin generally is well tolerated, but adverse effects may include nausea, vomiting, dizziness, headache, rash, diarrhea, drowsiness, and stomach pain.
- There are no reported drug interactions with guaifenesin.
- Guaifenesin is contraindicated in patients with a known hypersensitivity to the medication.
- Guaifenesin is not indicated for chronic cough associated with chronic lower respiratory tract diseases such as asthma, chronic obstructive pulmonary disease, or emphysema, or for smoker's cough.

Note About Pediatric Dosing

Manufacturers of cough and cold medications have revised product labeling to state that these products should not be used in children younger than 4 years. Health care providers should emphasize this information to caregivers of infants and young children.

Evaluation of Patient Outcomes for Cough

For most patients with cough who are candidates for selfmanagement, 7 days of nonprescription drug therapy should relieve cough. If, after 7 days of self-management, the cough persists but has lessened in severity, the patient may continue the self-management regimen until the cough resolves. Cough associated with viral URTIs usually resolves within 2 weeks but may persist for 3 weeks or longer. Cough associated with other respiratory infections typically resolves in 3–4 weeks. In all cases, the patient should be referred for further medical evaluation if the cough worsens or if other exclusions for self-treatment become apparent ([Figure 12–1](#)).

Key Points for Cough

- Cough is an important respiratory defensive reflex.
- Antitussives (cough suppressants) are the drugs of choice for treatment of nonproductive cough.
- Protussives (expectorants) are the drugs of choice for treatment of cough associated with thick, tenacious secretions expelled from the lungs with difficulty.
- Antitussives, expectorants, antihistamines, and nonsteroidal anti-inflammatory drugs have not been shown to be effective for acute cough associated with viral URTIs in either adults or children.
- In 2008, manufacturers voluntarily updated labels for cough and cold products to state “do not use” in children younger than 4 years of age.
- In 2018, FDA limited the use of prescription opioid cough and cold medicines to adults 18 years of age and older.
- Combination products are convenient but generally are more expensive per dose and are associated with increased risk of adverse effects and drug interactions.

- Referral to a primary care provider is warranted if the cough worsens or if signs or symptoms of a medical condition requiring further evaluation develop.
- Referral to a primary care provider also is warranted for patients with cough and a history or symptoms suggestive of a chronic underlying disease (e.g., asthma, COPD, chronic bronchitis, heart failure).

Chapter 13: Heartburn and Dyspepsia

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Editor's Note: This chapter is based on the 19th edition chapter of the same title, written by Tara Whetsel and Ann Zweber.

Heartburn (pyrosis), one of the most common gastrointestinal (GI) complaints, is often described as a burning sensation in the stomach or lower chest that extends up toward the neck and occasionally to the back.¹ Patients also may describe it as indigestion, acid regurgitation, sour stomach, or bitter belching. Heartburn is the main symptom of gastroesophageal reflux disease (GERD), but similar symptoms also may occur in patients with peptic ulcer disease (PUD), delayed gastric emptying, gallbladder disease, or numerous other GI disorders. *Dyspepsia*, defined as symptoms originating from the gastroduodenal region, may manifest as bothersome postprandial fullness, early satiation, epigastric pain, or epigastric burning.² Patients with dyspepsia may report many of these symptoms, as well as anorexia, belching, nausea, vomiting, or upper abdominal bloating. Heartburn and regurgitation also can occur with dyspepsia. Dyspepsia can be organic (i.e., has an identifiable cause) or functional (i.e., has no identifiable organic, systemic, or metabolic disease that is likely to explain the dyspeptic symptoms).

Although reflux-related disturbances are rarely a cause of death, dyspepsia, heartburn, and GERD are associated with considerable morbidity, complications, and cost. Patients with GERD have a decreased quality of life, with symptoms often affecting activity, work, and sleep.^{1,3} Patients with heartburn may limit their activities and restrict food choices to reduce symptom frequency and severity. Nocturnal symptoms may impair a patient's functioning the next day owing to poor sleep quality.^{1,3,4} Patients with intense GERD symptoms miss an average of 2 hours of work per week as a direct result of their symptoms.¹ In 2014 there were over 5.2 million office visits for GERD.⁵ Health care expenditures for esophageal disorders were \$18.1 billion in 2015, with 54% accounted for by prescription medications.⁵ Consumers spent over \$2.6 billion in 2017 on nonprescription heartburn medications.⁶

The prevalence rates for heartburn and acid regurgitation (as reported over a 1-year period) in a healthy, predominantly white population were 42% and 45%, respectively.¹ Weekly symptoms were reported by 20% of the respondents.¹

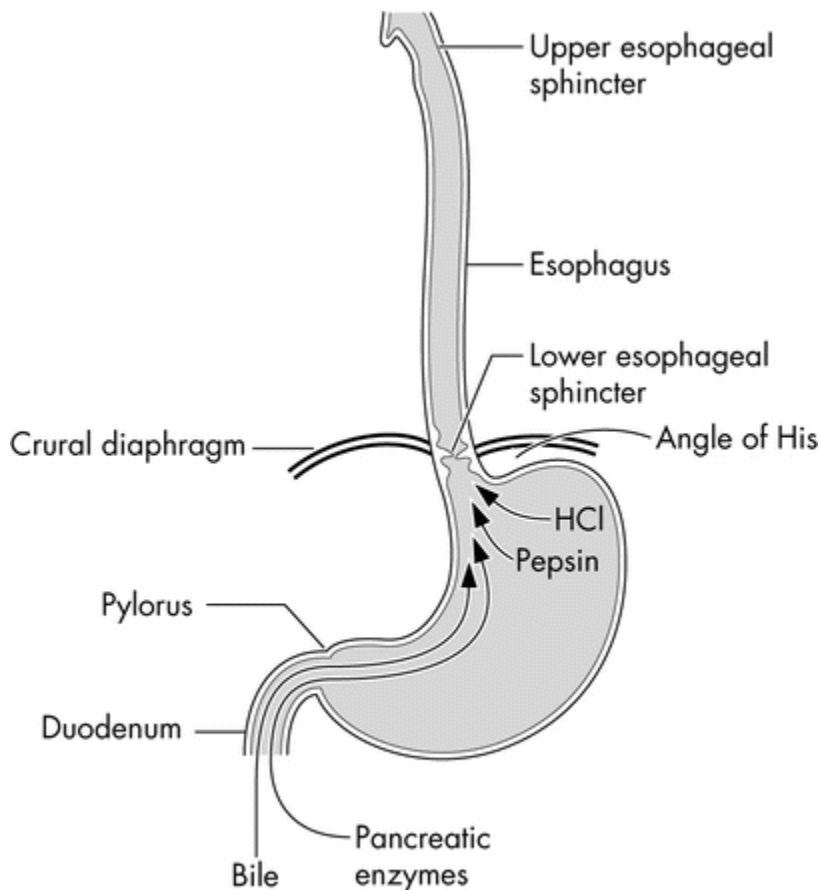
Most subjects reported their heartburn to be moderate in severity, which was defined in the study as a level that cannot be ignored but does not affect lifestyle. A survey in an urban American city found that 50% of Hispanics, 37% of Caucasians, 31% of African Americans, and 20% of Asians experienced heartburn at least monthly.¹ Although men and women are affected almost equally by GERD, rates of esophagitis and Barrett's esophagus (a precancerous condition) are higher among male patients.³ GERD complications also are more frequent among older persons, but this population may experience fewer symptoms because they have decreased sensitivity to refluxed acid. The prevalence of GERD has been increasing in Western countries over the past 30 years, which parallels the increase in obesity within these regions.¹ Heartburn is common during pregnancy, with 30%–80% of women complaining of heartburn.¹

The reported prevalence of dyspepsia varies, ranging between 10% and 45%.² Much of this variation is influenced by criteria used to define dyspepsia. When heartburn is excluded, the prevalence of uninvestigated dyspepsia is 5%–15%.² Compared with men, women have a slightly higher prevalence. The incidence of dyspepsia has been estimated at 1%–6% per year.² Among patients with dyspepsia, 5%–10% also have a peptic ulcer and 20%–25% have erosive esophagitis.² The estimated annual health care expenditure in the United States for dyspepsia is over \$18 billion, and societal costs are thought to be double this amount.⁷ An estimated 2%–5% of patients miss work because of symptoms associated with this disorder.⁷

Pathophysiology of Heartburn and Dyspepsia

Esophageal defense mechanisms—antireflux barriers, esophageal acid clearance, and tissue resistance—help protect the esophageal mucosa from acid damage.¹ Antireflux barriers include the intrinsic lower esophageal sphincter (LES), the diaphragmatic crura, the intra-abdominal location of the LES, the phrenoesophageal ligaments, and the acute angle of His ([Figure 13–1](#)). These anatomic structures and features work together to provide a physical barrier against reflux of gastric contents into the esophagus. The major component is the LES, which is contracted at rest but relaxes on swallowing to permit the flow of food, liquids, and saliva into the stomach. Transient relaxations occur when there is no swallowing or esophageal peristalsis, allowing retrograde movement of stomach contents into the esophagus. The

crural diaphragm provides an extrinsic squeeze to the LES, contributing to resting pressure and augmenting LES contractile function during periods of increased abdominal pressure, such as with coughing, sneezing, or bending over. The angle of His creates a flap valve effect that contributes to the antireflux barrier.



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Figure 13–1 Esophageal defense mechanisms—specifically, anatomic antireflux barriers—and physiologic factors associated with heartburn.

When reflux of acidic gastric material does occur, physiologic mechanisms help protect the esophageal mucosa from damage.¹ Esophageal acid clearance occurs when peristalsis moves refluxed material into the stomach, and saliva and esophageal gland secretions neutralize residual acid. Gravity also helps clear the esophagus. Tight junctions in esophageal mucosa and the intercellular space matrix further reduce epithelial damage from hydrogen ions. Epithelial cells also are capable of buffering and extruding hydrogen ions

that do penetrate the cell membrane. Tissue resistance is further aided by the esophageal blood supply, which delivers oxygen, nutrients, and bicarbonate, and removes hydrogen and carbon dioxide, thereby maintaining normal tissue acid–base balance. Even though gastroesophageal reflux is common, particularly postprandially, symptoms and esophageal damage are uncommon because of these esophageal defense mechanisms.⁸

Heartburn is likely related to stimulation of esophageal mucosal chemoreceptors.⁸ Acid reflux, weakly acidic reflux, bile reflux, and mechanical stimulation of the esophagus can cause heartburn symptoms.^{1,8} It is unclear why some reflux episodes produce symptoms while most do not. Possible contributing factors include mucosal disruption, decreased acid clearance, inflammation, reduced salivary bicarbonate concentration, volume of refluxate, frequency of heartburn, and interaction of pepsin with acid.⁸ One theory is that the esophagus becomes hypersensitive from repeated acid exposure, causing symptoms to occur with smaller boluses of acid.⁸

Any disruption in the esophageal defense mechanisms can lead to increased acid exposure. Distention of the proximal stomach by either food or gas is a major stimulus for transient LES relaxation episodes. Some patients may have decreased LES pressure that can be overcome by an abrupt increase in intra-abdominal pressure from coughing, straining, or bending over. A hiatal hernia occurs when the upper part of the stomach pushes upward through the diaphragm. The resultant mass effect impairs LES function and esophageal acid clearance. A hiatal hernia displaces the LES from the crural diaphragm, reduces LES pressure, and results in more frequent transient relaxations of the LES, all of which contribute to increased reflux. Although the role of a hiatal hernia in GERD is unclear, its presence is a recognized contributing factor in patients with Barrett's esophagus and esophageal cancer.

Prolonged exposure of esophageal tissue to refluxed material can occur in a lying or sleeping position, with decreased salivation, or with peristaltic dysfunction. Although the impact of delayed gastric emptying is controversial, large volumes of refluxate from delayed gastric emptying or overeating also can increase esophageal acid exposure. The resulting damage to the tight intercellular junctions of the esophageal mucosa can lead to increased cellular permeability to hydrogen ions, with subsequent cellular injury. This increased permeability partly explains the development of heartburn in the absence of overt esophagitis.¹ The composition of the refluxate is an important

determinant of the degree of esophageal damage. Pepsin and/or bile salts combined with acid produce greater injury than that seen with acid alone. *Helicobacter pylori* infection lowers gastric acidity, thereby possibly protecting against development of heartburn, GERD, and related complications.¹

A number of risk factors are weakly associated with the occurrence of heartburn (Table 13–1).^{1,8–12} Foods (e.g., fat, chocolate, peppermint) and medications (e.g., theophylline, morphine, calcium channel blockers, diazepam) can decrease LES pressure, leading to increased reflux. Citrus, tomato-based, and spicy foods irritate inflamed esophageal mucosa. Tobacco smoke contributes to heartburn by relaxing LES pressure and decreasing salivation. Anxiety, fear, and worry may lower visceral sensitivity thresholds, leading to increased pain perception. Bending over, straining to defecate, lifting heavy objects, and performing isometric exercises may increase intra-abdominal pressure above the LES pressure, leading to reflux. Obesity increases intra-abdominal pressure, and epidemiologic studies suggest that the prevalence of GERD is considerably higher in obese patients.¹ Central obesity, as measured by waist-to-hip ratio, may be a better predictor for the development of GERD than body mass index (BMI).¹ Daytime naps are associated with increased esophageal acid exposure and symptoms compared with nocturnal sleep.⁴ Sleeping on the right side is associated with increased reflux.⁸ Genetics also may play a role in the development of GERD, as family clustering of GERD along with its complications has been reported.¹

Table 13–1 Risk Factors That May Contribute to Heartburn and GERD

Dietary	Medications
Alcohol (ethanol)	Alpha-adrenergic antagonists
Caffeinated beverages	Anticholinergic agents
Carbonated beverages	Aspirin/other NSAIDs
Chocolate	Barbiturates
Citrus fruit or juices	Benzodiazepines
Coffee	Beta ₂ -adrenergic agonists
Fatty foods	Bisphosphonates
Garlic or onions	Calcium channel blockers

Mint (e.g., spearmint, peppermint)	Chemotherapy
Spicy foods	Dopamine
Sugars	Doxycycline
Tomatoes/tomato juice	Estrogen
Lifestyle	Iron
Emotions (anxiety, fear, worry)	Narcotic analgesics
Exercise (isometric, running)	Nitrates
Obesity	Oral contraceptives
Smoking (tobacco)	Potassium
Stress	Progesterone
Supine body position	Prostaglandins
Tight-fitting clothing	Quinidine
Diseases	TCA's
Insulin resistance (e.g., pre-diabetes, diabetes, PCOS)	Tetracycline
Motility disorders (e.g., gastroparesis)	Theophylline
PUD	Zidovudine
Scleroderma	Other
Sjögren disease	Genetics
Zollinger–Ellison syndrome	Pregnancy

Key: GERD = Gastroesophageal reflux disease; NSAIDs = nonsteroidal anti-inflammatory drugs; PUD = peptic ulcer disease; TCAs = tricyclic antidepressants.

Source: [References 1](#) and [8–12](#).

Dyspepsia may be caused by PUD, GERD, celiac disease (rarely), gastric or

esophageal malignancy (rarely), or other GI disorders. Specific foods (e.g., spicy food, coffee, alcohol) and excessive food intake have not been established as causing dyspepsia. However, certain medications (e.g., iron, antibiotics, narcotics, digoxin, estrogens and oral contraceptives, theophylline, levodopa, nonsteroidal anti-inflammatory drugs [NSAIDs]) commonly cause dyspepsia through direct gastric mucosal injury, changes in GI function, exacerbation of reflux, or some other mechanism.² The pathophysiology of functional dyspepsia is unclear but may include delayed gastric emptying, impaired gastric accommodation to food intake, hypersensitivity to gastric distention, altered duodenal sensitivity, abnormal intestinal motility, or central nervous system dysfunction.² One or more of these disturbances can occur in individual patients. The cause of symptoms in patients with functional dyspepsia has not been established, but population studies have suggested a genetic predisposition, infectious factors, and psychological components. *H. pylori* may play a role in functional dyspepsia, as evidenced by a small improvement in symptoms after eradication of the infection.

Patients who have recovered from gastroenteritis may suffer from postinfection functional dyspepsia. Psychosocial factors are an important contributor to symptom severity. Patients with functional dyspepsia also may have anxiety disorders, depression, somatoform disorders, or a recent or remote history of physical or sexual abuse. The exact mechanism is unknown, but some studies have suggested a relationship between psychosocial factors and visceral hypersensitivity.²

Clinical Presentation of Heartburn and Dyspepsia

Heartburn may occur alone or as a symptom of other GI disorders, such as GERD or PUD ([Table 13–2](#)). Heartburn is noted most frequently within 1 hour after eating, especially after a large meal, or with ingestion of offending foods or beverages. Lying down or bending over may exacerbate heartburn. Regurgitation and, less commonly, water brash may occur. Regurgitation is characterized by a bitter acidic fluid in the back of the throat; this phenomenon occurs more commonly after meals, at night, or upon bending over. It differs from vomiting in that nausea, retching, or abdominal contractions do not occur.^{1,8} *Water brash* is the sudden filling of the mouth

with clear, slightly salty fluid secreted from the salivary glands. Burping, hiccups, nausea, and vomiting are less common signs and symptoms that may occur with heartburn. Severity with any of these problems is subjective, and no standard definitions exist for classifying symptoms as “mild,” “moderate,” or “severe.” In general, symptoms may be considered *mild* if they bother the patient a little but do not interfere with normal activities. Symptoms that are somewhat bothersome or annoying, or that interfere with normal activities, may be considered *moderate*. Heartburn symptoms that occur two or more times per week are suggestive of GERD.¹ GERD can be complicated by erosive esophagitis, hemorrhage, esophageal ulcers, strictures, Barrett’s esophagus, and esophageal adenocarcinoma. Heartburn severity is poorly correlated with esophageal damage, especially in older patients who on presentation may have no or mild symptoms despite severe erosive esophagitis or other complications.¹ Upper endoscopy is the standard for determining the presence and extent of esophageal damage.

Table 13–2 Differentiation of Simple Heartburn From Other Acid-Related Disorders

	Simple Heartburn	GERD	Dyspepsia	PUD
Etiology	See Table 13–1 .	See Table 13–1 .	Possible contributing factors: food, alcohol, caffeine, stress, and medications Chronic dyspepsia: associated with PUD, GERD, celiac disease, and gastric cancer; or lacking an identifiable cause (functional dyspepsia)	Gastric or duodenal ulcer caused most commonly by <i>Helicobacter pylori</i> infection and/or NSAID use
Typical symptoms	Burning sensation behind the breastbone that may radiate toward the neck, throat, and, occasionally, the back	Heartburn, acid regurgitation	Primary: postprandial fullness, early satiation, epigastric pain, epigastric burning Other: belching, bloating, nausea, vomiting	Gnawing or burning epigastric pain, occurring during day and frequently at night; may be accompanied by heartburn and dyspepsia

Key: GERD = Gastroesophageal reflux disease; NSAID = nonsteroidal anti-inflammatory drug; PUD = peptic ulcer disease.

“Alarm symptoms” include dysphagia, odynophagia, vomiting, GI bleeding, and unexplained weight loss. These severe signs and symptoms can indicate more serious disease and/or complications. *Dysphagia* (difficulty swallowing) is slowly progressive for solid food and usually is associated with long-standing heartburn. The most common cause is peptic stricture or Schatzki’s ring, but severe esophagitis, peristaltic dysfunction, and esophageal cancer are other potential etiologic conditions.¹ *Odynophagia* (painful swallowing) is less common and may indicate severe ulcerative esophagitis, pill-induced injury (e.g., from tetracycline, potassium chloride, vitamin C, NSAIDs including aspirin, or bisphosphonates), or infection. Signs of GI bleeding include hematemesis, melena, occult bleeding, and anemia. Patients also may present with atypical or extraesophageal signs and symptoms related to gastroesophageal reflux. These include noncardiac chest pain, asthma, laryngitis, hoarseness, *globus sensation* (subjective sensation of a lump in the throat), chronic cough, recurrent pneumonitis, disordered sleep, and dental erosion.^{1,8} Alarm symptoms or atypical symptoms warrant evaluation by a primary care provider, with likely referral to a gastroenterologist.

Dyspepsia can manifest with one or more of four main symptoms. *Postprandial fullness* is an unpleasant sensation perceived as the prolonged persistence of food in the stomach. *Early satiation* (early satiety) is the feeling of fullness that occurs soon after eating begins and that is out of proportion to the amount of food ingested.² *Epigastric pain* is an unpleasant sensation between the umbilicus and lower end of the sternum. *Epigastric burning* refers to an unpleasant, subjective sensation of heat. Less specific manifestations may include bloating, nausea, vomiting, or belching. Symptoms are mostly intermittent and may or may not be related to meals. Weight loss is considered an alarm symptom that should prompt referral for further investigation. Other alarm symptoms include anemia, blood loss, and dysphagia.²

Algorithm: Heartburn

Figure 13–2 Self-care for heartburn. Key: H2RA = Histamine type 2 receptor antagonist; OTC = over-the-counter; PPI = proton pump inhibitor.

Treatment of Heartburn and Dyspepsia

Treatment Goals

The goals of self-treatment for heartburn and dyspepsia are (1) to provide complete relief of symptoms, (2) to reduce recurrence of symptoms, and (3) to prevent and manage unwanted effects of medications.

General Treatment Approach

The approach to self-treatment for heartburn and dyspepsia requires an initial assessment to determine whether the patient is a candidate for self-care (Figure 13–2). Patients with exclusions for self-treatment should be referred for further medical evaluation. When self-treatment is deemed appropriate, specific nondrug measures discussed in the section “Nonpharmacologic Therapy” should be recommended and continued throughout treatment. If indicated, a recommendation also should be made for a nonprescription medication. The selection of the medication should be based on frequency, duration, and severity of symptoms; the cost of the medication; potential drug–drug interactions and adverse effects; and the patient’s preference. Antacids or nonprescription histamine type 2 (H_2) receptor antagonists (H2RAs) should be recommended for patients with mild to moderate, infrequent heartburn or dyspepsia. Antacids are advantageous because they provide rapid relief of symptoms, but relief is short-lived when antacids are taken on an empty stomach (Table 13–3). When used in recommended doses, the different types of antacids are interchangeable despite differences in component salts and potency. Antacid/alginic acid combinations are more effective than antacids alone in reducing heartburn symptoms.^{12,13}

Table 13–3 Onset and Duration of Symptomatic Relief With Nonprescription Medications for Relieving Heartburn

Medication	Onset of Relief	Duration of Relief
Antacids	<5 minutes	20–30 minutes ^a
H2RAs	30–45 minutes	4–10 hours
H2RA + antacid	<5 minutes	8–10 hours
PPIs	1–3 hours	12–24 hours

^a Food prolongs duration of relief.

Key: H2RA = Histamine type 2 receptor antagonist; PPIs = proton pump inhibitors.

A nonprescription H2RA is preferable to an antacid when patients with mild to moderate episodic heartburn require more prolonged relief of symptoms. H2RAs do not relieve heartburn or dyspepsia as rapidly as antacids do ([Table 13–3](#)), but they may be used with an antacid if both quick relief and longer duration of action are desired. H2RAs also may be used to prevent heartburn and acid indigestion if they are given 30 minutes to 1 hour before situations in which heartburn is anticipated. Lower dose nonprescription H2RA products (e.g., famotidine 10 mg up to twice daily) should be recommended for patients with mild, infrequent heartburn. Higher dose nonprescription products (e.g., famotidine 20 mg up to twice daily) should be reserved for moderate symptoms. Patients should not exceed 14 days of self-treatment with an antacid or H2RA without consulting their primary care provider.

Nonprescription proton pump inhibitors (PPIs) can be used for treating frequent heartburn (occurring ≥ 2 days per week).¹⁴ PPIs work best when taken daily, unlike antacids and H2RAs, which are taken as needed. The onset of symptomatic relief after a PPI dose is slower than with an H2RA dose ([Table 13–3](#)), and complete relief of symptoms may take several days after initiation of therapy. However, compared with H2RAs, PPIs provide better symptomatic relief, with a prolonged duration of action. Self-treatment with a PPI should be limited to a duration of 14 consecutive days and retreatment to every 4

months.¹⁵

Nonpharmacologic Therapy

Lifestyle and dietary modifications are often recommended for management of heartburn or dyspepsia despite a lack of evidence for most interventions.^{1,8–10} Weight loss is associated with reduced esophageal acid exposure and should be recommended to obese patients as well as patients with recent weight gain. Weight loss of 10% can lead to a significant decrease in symptoms of heartburn, regurgitation, and belching.¹⁰ Patients with nocturnal symptoms should avoid eating within 2–3 hours of bedtime and sleep on their left side. Elevating the head of the bed by placing 6- to 8-inch blocks underneath the legs at the head of the bed or placing a foam wedge (e.g., GERD pillow) beneath the patient's upper torso and head also is beneficial. Use of traditional pillows to elevate the upper torso may worsen symptoms because they cause the patient to bend at the waist, which contributes to an increase in intragastric pressure. Smoking cessation reduces symptoms in normal-weight subjects but has not been shown to result in the same improvements in obese patients.¹⁰ Owing to numerous health benefits, however, smoking cessation should be encouraged for all patients regardless of weight. A Mediterranean diet (high intake of vegetables, legumes, fruits, whole grains, fish, and olive oil; low intake of red or processed meat) also is associated with lower risk for development of GERD symptoms.¹⁰

Current evidence does not support advising all patients to avoid all foods and beverages listed in [Table 13–1](#).^{1,8–11} Patients should be advised to keep a symptom diary to help determine foods, beverages, and activities that correlate with symptom onset and severity. Lifestyle and dietary modifications can then be made to avoid “triggers.” Prescription and nonprescription medications should be evaluated for their potential to cause or exacerbate heartburn and dyspepsia ([Table 13–1](#)). When other options are available, patients should be advised to switch to less troublesome nonprescription medications; they also should consult their prescriber about prescription drugs that may be exacerbating their symptoms. See the box “Patient Education for Heartburn and Dyspepsia” for additional strategies that may be helpful in preventing or reducing symptoms.

Pharmacologic Therapy

Antacids

Antacids relieve heartburn and dyspepsia by neutralizing gastric acid. Nonprescription antacid products contain at least one of the following salts: magnesium (hydroxide, carbonate, or trisilicate); aluminum (hydroxide or phosphate); calcium carbonate; or sodium bicarbonate ([Table 13–4](#)). Most antacids are relatively inexpensive, making them affordable products for the temporary relief of mild and infrequent heartburn and dyspepsia.

Table 13–4 Selected Nonprescription Antacid and Bismuth Products and Their Dosage Regimens

Trade Name	Primary Ingredient(s)	Dosage (maximum daily dosage)
Adults/Children ≥ 12 Years		
Alka-Seltzer Heartburn	Sodium bicarbonate 1940 mg; anhydrous citric acid 1000 mg	Dissolve 2 tablets in 4 ounces of water every 4 hours PRN (8 tablets)
Alka-Seltzer Original	Sodium bicarbonate 1916 mg; anhydrous citric acid 1000 mg; aspirin 325 mg	Dissolve 2 tablets in 4 ounces of water every 4 hours PRN (8 tablets)
Gaviscon Extra Strength Liquid	Each 5 mL contains ^a aluminum hydroxide 254 mg; magnesium carbonate 237.5 mg	10–20 mL 4 times a day, after meals and at bedtime PRN (80 mL)
Gelusil Tablets	Aluminum hydroxide 200 mg; magnesium hydroxide 200 mg; simethicone 25 mg	Chew 2–4 tablets; repeat hourly if symptoms return (12 tablets)
Mylanta Maximum Strength Liquid	Each 10 mL contains aluminum hydroxide 800 mg; magnesium hydroxide 800 mg; simethicone 80 mg	10–20 mL between meals and at bedtime PRN (60 mL)
Pepto-Bismol Ultra Liquid	Each 15 mL contains bismuth subsalicylate 525 mg	15 mL every 30 minutes PRN (8 doses or 120 mL)
Pepto-Bismol Chewable Tablets	Bismuth subsalicylate 262 mg	Chew or dissolve in mouth 2 tablets every 30–60 minutes PRN (8 doses or 16 tablets)
Rolaids Regular	Calcium carbonate 550 mg; magnesium hydroxide 110 mg	Chew 2–4 tablets PRN (12 tablets)

Trade Name	Primary Ingredient(s)	Dosage (maximum daily dosage)
Strength Tablets		
Tums Extra Strength 750 Tablets	Calcium carbonate 750 mg	Chew 2–4 tablets PRN (10 tablets)
Tums Chewy Delights Soft Chews	Calcium carbonate 1177 mg	Chew 2–3 soft chews PRN (6 soft chews)
Children ≤ 12 Years		
Pepto Kids Chewable Tablets	Calcium carbonate 400 mg	Age 2–5 years: 1 tablet (3 tablets)
		Age 6–11 years: 2 tablets (6 tablets)

^a Sodium alginate (alginic acid) is listed as an inactive ingredient.

Key: PRN = As needed—*pro re nata* (L., “as the need arises”).

Antacids act as buffering agents in the lower esophagus, gastric lumen, and duodenal bulb and increase LES pressure.¹ The cations react with chloride, but the anionic portion of the molecule reacts with hydrogen ions to form water and other compounds. Sodium bicarbonate reacts rapidly with gastric acid to form sodium chloride, carbon dioxide, and water. This agent’s duration of action is shortened by its quick elimination from the stomach.¹⁶ Of the magnesium salts, magnesium hydroxide is used most often. Magnesium hydroxide reacts rapidly with gastric acid to form magnesium chloride and water. This agent has a shorter duration of action than that of calcium carbonate and aluminum hydroxide. Calcium carbonate is a potent antacid that dissolves slowly in gastric acid to form calcium chloride, carbon dioxide, and water. This agent’s onset of action is slower but its duration of effect is longer than that of magnesium hydroxide or sodium bicarbonate. Aluminum hydroxide reacts with hydrochloric acid to form aluminum chloride and water. This agent has a slower onset and a longer duration than for magnesium

hydroxide. As a result of these reactions, a small but noticeable increase in intragastric pH occurs.

Compared with tablets, liquid antacids usually have a faster onset of action, because they are already dissolved or suspended, allowing contact with a maximal surface area for action. Of the tablet dosage forms, the quick-dissolving antacid tablets may provide the most rapid relief of symptoms. The duration of action for all antacids is transient, lasting only as long as the antacid remains in the stomach. The presence of food affects the duration of action of antacids. When these agents are administered on an empty stomach, relief can last for 20–60 minutes. When taken within 1 hour after a meal, antacids may remain in the stomach for up to 3 hours.¹⁶

Differences in efficacy, onset, duration, and adverse effects of antacids are determined primarily by the cation, specific salt, and potency. Antacid potency is based on the number of milliequivalents of *acid-neutralizing capacity* (ANC), defined as the amount of acid buffered per dose over a specified period of time. Factors that contribute to the ANC include product formulation, ingredients, and concentration.¹⁶ Consequently, the ANC is product-specific; the same number of antacid tablets or equal volumes of different liquid antacids are not necessarily equal in potency.

Most antacids are absorbed minimally into the systemic circulation.¹⁶ Approximately 90% of calcium is converted to insoluble calcium salts; the remaining 10% is absorbed systemically. About 15%–30% of magnesium and 17%–30% of aluminum may be absorbed and then excreted renally; therefore, accumulation may occur in patients with renal insufficiency. Sodium bicarbonate is absorbed readily and is eliminated renally.

Antacids are indicated for the treatment of mild, infrequent heartburn, sour stomach, and acid indigestion. Combination products containing aspirin or acetaminophen are approved by the U.S. Food and Drug Administration (FDA) for overindulgence in food and drink and for hangover, although product effectiveness has not been demonstrated. Patients with mild dyspepsia may experience some relief with antacids, but no studies demonstrate their effectiveness for this disorder.²

Antacids are administered orally. The effective dose of an antacid varies depending on product ingredients, milliequivalents of ANC, formulation, and the frequency and severity of symptoms. Patients should be instructed to take

product-specific recommended doses at the onset of symptoms. Dosing may be repeated in 1–2 hours, if needed, but should not exceed the maximum daily dosage for a particular product ([Table 13–4](#)). Patients should be reevaluated if antacids are used more than twice a week or regularly for more than 2 weeks. Frequent antacid users may need to be switched to a longer-acting product, such as an H2RA, an H2RA plus an antacid, or a PPI, or referred to an appropriate health care provider.

Antacids usually are well tolerated. Adverse effects generally are related to the specific cation. The most common adverse effect associated with magnesium-containing antacids is dose-related diarrhea. The occurrence of diarrhea may be reduced by combining magnesium-containing antacids with aluminum hydroxide. However, when higher dosages of this combination are used, the predominating adverse effect is diarrhea. Magnesium excretion is impaired in patients with renal disease, which may result in systemic accumulation of magnesium. Magnesium-containing antacids should not be used in patients with a creatinine clearance of less than 30 mL/minute.¹⁶

Aluminum-containing antacids are associated with dose-related constipation. Aluminum hydroxide binds dietary phosphate in the GI tract, increasing phosphate excretion in the feces. Frequent and prolonged use of aluminum hydroxide may lead to hypophosphatemia.¹⁶ Chronic use of aluminum-containing antacids in patients with renal failure may lead to aluminum toxicity and should be avoided.

Calcium carbonate may cause belching and flatulence as a result of carbon dioxide production. Constipation occurring during use of calcium antacids has been reported, but little evidence is available to support this correlation. Calcium stimulates gastric acid secretion and is hypothesized to cause increased acidity when calcium-containing antacids are used to treat acid-related disorders. The clinical importance of this finding, however, remains uncertain.¹⁶ If renal elimination is impaired, hypercalcemia may occur, and accumulation of calcium may result in the formation of renal calculi. Because many antacids have been reformulated to contain calcium, there is a risk of hypercalcemia when high and frequent dosages of calcium-containing antacids are taken with other calcium supplements or foods such as milk or orange juice with added calcium. The upper limit for calcium intake for adults with normal renal function is 2500 mg/day for those 19–50 years of age and 2000 mg/day for those 51 years of age and older.¹⁷ (See [Chapter 23](#) for a

discussion of calcium supplementation.)

Sodium bicarbonate frequently causes belching and flatulence that result from the production of carbon dioxide.¹⁶ The high sodium content (274 mg sodium/g sodium bicarbonate) may cause fluid overload in patients with congestive heart failure, renal failure, cirrhosis, or pregnancy, and in those on sodium-restricted diets. Patients with normal renal function excrete additional bicarbonate, whereas patients with impaired renal function retain bicarbonate, which may cause systemic alkalosis. A high intake of calcium along with an alkalinizing agent (e.g., sodium bicarbonate, calcium carbonate) may lead to development of hypercalcemia, alkalosis, irritability, headache, nausea, vomiting, weakness, and malaise (milk–alkali syndrome).¹⁶ Patients who take calcium supplements should avoid using sodium bicarbonate as an antacid. Antacid–aspirin combination products can increase the risk of serious bleeding and should be avoided in patients with bleeding risks or salicylate sensitivities. (For a complete discussion of salicylate risk, see [Chapter 5](#).) [Table 13–5](#) lists clinically significant drug–drug interactions.^{18–23}

Table 13–5 Clinically Important Drug–Drug Interactions With Nonprescription Heartburn and Dyspepsia Agents

Antacid/Acid Reducer	Drug(s)/Drug Class	Potential Interaction	Management/ Preventive Measures
Antacids	Itraconazole, ketoconazole, iron, atazanavir	Increased gastric pH may decrease disintegration, dissolution, or ionization of drug leading to decreased absorption.	Separate doses by at least 2 hours.
	Amphetamines	Absorption of amphetamines is increased and excretion decreased.	Avoid concurrent use or monitor response to therapy.
	Rosuvastatin	Absorption of rosuvastatin is decreased	Separate doses by at least 2 hours. Infrequent use of antacids is unlikely to cause clinically significant interaction.
	Enteric-coated medications	Increased gastric pH may cause premature breakdown of enteric	Separate doses by at least 2 hours.

Antacid/Acid Reducer	Drug(s)/Drug Class	Potential Interaction	Management/ Preventive Measures
		coating.	
Calcium carbonate, magnesium hydroxide, aluminum hydroxide	Levothyroxine	Absorption of levothyroxine is delayed or impaired.	Separate doses by at least 4 hours.
	Tetracyclines	Absorption of antibiotic is decreased.	Separate doses by at least 4 hours.
	Fluoroquinolones	Absorption of antibiotic is decreased.	Take antibiotic 2 hours before or 6 hours after taking antacid.
Magnesium hydroxide, aluminum hydroxide	Azithromycin	Absorption of antibiotic is decreased.	Separate doses by at least 2 hours.
Sodium bicarbonate	Quinidine	Increased urinary pH may decrease renal excretion of quinidine.	Avoid concurrent use or monitor response to therapy.
	Salicylates	Increased urinary pH may increase renal excretion of salicylates.	Avoid concurrent use or monitor for decreased response to salicylates.
Antacids, H2RAs, PPIs	Erlotinib, dasatinib, gefitinib, other TKIs, rilpivirine, ledipasvir/sofosbuvir	Increased gastric pH decreases absorption	Avoid concurrent use of PPI or H2RA; separate from antacids by several hours
H2RAs, PPIs	Itraconazole, ketoconazole, atazanavir, iron sulfate, calcium carbonate	Increased gastric pH may decrease disintegration, dissolution, or ionization of drug, leading to decreased absorption.	Avoid concurrent use or monitor response to therapy.
Cimetidine	Phenytoin, warfarin, amiodarone, clopidogrel, nifedipine, theophylline, tricyclic	Cimetidine inhibits CYP450 1A2, 2C19, and to a lesser extent, 2D6, 3A4.	Avoid use of cimetidine in patients taking medications metabolized by these CYP enzymes.

Antacid/Acid Reducer	Drug(s)/Drug Class	Potential Interaction	Management/ Preventive Measures
	antidepressants, others		
Cimetidine, esomeprazole, lansoprazole, omeprazole	Citalopram	Inhibition of CYP450 2C19 increases citalopram concentrations and dose-dependent risk of QT prolongation.	Citalopram dose should not exceed 20 mg per day if used concomitantly.
PPIs	Warfarin, theophylline, tacrolimus, mycophenolate mofetil	PPI inhibition of CYP2C19 may result in increased concentrations of target drugs.	Avoid concurrent use or check with prescriber.
	Digoxin	PPIs may increase digoxin absorption.	Check with prescriber before use.
	Methotrexate	Concurrent use increases risk of toxicity of methotrexate.	Avoid concurrent use of high-dose methotrexate. Clinically significant toxicity is unlikely with lower weekly doses.
Omeprazole, esomeprazole	Clopidogrel	Inhibition of variants of CYP2C19 reduces conversion of clopidogrel to its active form.	Avoid concurrent use or check with prescriber. Clinically significant interaction is unlikely.
	Cilostazol, diazepam	Inhibited metabolism may result in increased concentration of target drug.	Avoid concurrent use. Lansoprazole may be a safer alternative.

Key: CYP = Cytochrome P450; H2RA = histamine type 2 receptor antagonist; PPI = protein pump inhibitor; TKI = tyrosine kinase inhibitor.

Source: References [18–23](#).

Alginic acid reacts with sodium bicarbonate in saliva to form a viscous layer of sodium alginate that floats on the surface of gastric contents, forming a

protective barrier against esophageal irritation. Although alginic acid does not neutralize acid, the combination of alginic acid and an antacid provides better symptomatic relief than that obtained with the antacid alone.^{12,13} Because evidence supporting alginic acid's efficacy as a single agent is insufficient, FDA has not granted it Category I (generally recognized as safe and effective) status. However, alginic acid may be found as an inactive ingredient in several antacid preparations ([Table 13–4](#)). Some antacid products also contain simethicone to decrease discomfort related to intestinal gas. (See [Chapter 14](#) for a more detailed description of simethicone.)

Histamine Type 2 Receptor Antagonists

Cimetidine, ranitidine, famotidine, and nizatidine are approved for nonprescription use ([Table 13–6](#)). Nonprescription products containing nizatidine currently are not available in the United States. Since the autumn of 2019, FDA had been finding that many lots of nonprescription and prescription ranitidine, including the brand-name product Zantac, contained N-nitrosodimethylamine (NDMA), a probable human carcinogen. On April 1, 2020, FDA issued a decision requesting that all manufacturers of ranitidine immediately remove their products from the marketplace.²⁴ At the time of publication of this book, it was unknown when or whether ranitidine would return to the market. Any mention or reference to ranitidine in this chapter is informational only and does not indicate the product is available for purchase. When used in recommended dosages, the H₂RAs are considered interchangeable despite minor differences in potency, onset, duration of symptomatic relief, and adverse effects. H₂RAs reduce acid secretion by inhibiting histamine on the H₂ receptor of the parietal cell.¹² They are effective in relieving fasting and nocturnal symptoms. Their bioavailability is not affected by food but may be reduced modestly by antacids. Onset of symptomatic relief with H₂RAs is not as rapid as with antacids, but H₂RAs have a longer duration of effect ([Table 13–3](#)). Cimetidine is the shortest acting (4–8 hours); ranitidine, famotidine, and nizatidine have a somewhat longer duration of effect. Tolerance to the gastric antisecretory effect may develop when H₂RAs are taken daily (versus as needed) and may be responsible for diminished efficacy.^{1,12} Therefore, it is preferable to take an H₂RA on an as-needed basis rather than regularly, every day. All four H₂RA drugs are eliminated by a combination of renal and hepatic metabolism, with renal elimination being more important. A reduced daily H₂RA dose is recommended in patients with impaired renal function (creatinine clearance

<50 mL/minute).

Table 13–6 Selected Nonprescription H2RA and PPI Products and Dosage Regimens

Trade Name	Primary Ingredient(s)	Dosage (maximum daily dose)
H2RA Products (adults/children ≥ 12 years)		
Tagamet HB, various generic	Cimetidine 200 mg	1 tablet with a glass of water (2 tablets)
Pepcid AC, various generic	Famotidine 10 mg	1 tablet with a glass of water (2 tablets)
Pepcid AC Maximum Strength, various generic	Famotidine 20 mg	1 tablet with a glass of water (2 tablets)
Pepcid Complete, various generic	Famotidine 10 mg; calcium carbonate 800 mg; magnesium hydroxide 165 mg	Chew and swallow 1 tablet (2 tablets)
Zantac 75, various generic	Ranitidine 75 mg	1 tablet with a glass of water (2 tablets)
Zantac 150, various generic	Ranitidine 150 mg	1 tablet with a glass of water (2 tablets)
PPI Products (adults ≥ 18years)		
Prilosec OTC, various generic	Omeprazole magnesium 20.6 mg	1 tablet with a glass of water 30 minutes before morning meal; take daily for 14 days (1 tablet)
Zegerid, various generic	Omeprazole 20 mg; sodium bicarbonate 1100 mg	1 capsule with a glass of water 1 hour before morning meal; take daily for 14 days (1 capsule)
Prevacid 24HR, various generic	Lansoprazole 15 mg	1 capsule with a glass of water 30 minutes before morning meal; take daily for 14 days (1 capsule)
Nexium 24HR, various generic	Esomeprazole 20 mg	1 capsule with a glass of water 30 minutes before morning meal; take daily for 14 days (1 capsule)

Key: H2RA = Histamine type 2 receptor antagonist; PPI = proton pump inhibitor.

Nonprescription H2RAs are indicated for the treatment of mild to moderate infrequent or episodic heartburn and for the prevention of heartburn associated with acid indigestion and sour stomach. H2RAs are more effective than placebo for relief of heartburn and provide modest improvement in patients with mild, infrequent uninvestigated dyspepsia.^{1,2} These agents may be used at the onset of symptoms or 30–60 minutes before an event (e.g., meal, exercise) in which heartburn is anticipated. The combination H2RA–antacid product (Pepcid Complete [famotidine plus magnesium hydroxide and calcium carbonate]; [Table 13–6](#)) is indicated for patients with postprandial heartburn who have not premedicated with an H2RA. This combination product provides quick relief and a longer duration of effect. Self-treatment dosing should be limited to no more than 2 times a day. If routine self-treatment with an H2RA is needed for more than 2 weeks, medical referral is recommended.

H2RAs are well tolerated and are associated with a low incidence of adverse effects. The most common adverse effects reported with all four H2RAs are headache, diarrhea, constipation, dizziness, and drowsiness.

Thrombocytopenia is a rare but serious adverse effect associated with all four H2RAs, but this condition is reversible upon discontinuation of the drug.

Cimetidine is associated with a weak antiandrogenic effect; accordingly, when taken in high doses, it may result in decreased libido, impotence, or gynecomastia in men. [Table 13–5](#) lists drug-drug interactions for H2RAs.

Proton Pump Inhibitors

PPIs are potent antisecretory drugs that relieve heartburn and dyspepsia by decreasing gastric acid secretion. They inhibit hydrogen potassium ATPase (the proton pump), thereby irreversibly blocking the final step in gastric acid secretion and providing a more potent and prolonged antisecretory effect than that obtained with the H2RAs ([Table 13–3](#)).^{1,12} PPIs are rapidly absorbed after oral administration. The bioavailability of PPIs is increased with continued daily dosing but is reduced if taken after a meal compared to fasting. Onset of

symptomatic relief after an oral dose may occur in 1–3 hours, but complete relief may take 1–4 days.

Omeprazole magnesium 20.6 mg (Prilosec OTC) was the first PPI to become available for nonprescription use in the United States ([Table 13–6](#)). It is available as a delayed-release tablet containing enteric-coated pellets (for protection against intragastric degradation) and rapidly dissociates to omeprazole 20 mg. Immediate-release omeprazole (Zegerid) is formulated with omeprazole 20 mg and sodium bicarbonate 1100 mg. The sodium bicarbonate in Zegerid raises intragastric pH, permitting rapid absorption of omeprazole from the duodenum, but the available evidence is insufficient to confirm that this action results in a quicker onset of symptomatic relief. Esomeprazole magnesium 22.3 mg (Nexium 24HR) is the S-isomer of omeprazole and is available as a delayed-release capsule and tablet. Lansoprazole 15 mg (Prevacid 24HR) is available as a capsule formulation containing enteric-coated granules and as a delayed-release orally disintegrating tablet. Differences in efficacy among the PPIs have not been established. PPI tablets and capsules should not be chewed or crushed, because the enteric coating will be compromised, thereby decreasing the effectiveness of the drug.

Nonprescription PPIs are indicated for the treatment of frequent heartburn, defined as the occurrence of symptoms 2 or more days a week. These drugs are not intended for immediate relief of occasional or acute episodes of heartburn and dyspepsia. Because PPIs inhibit only those proton pumps that are actively secreting acid, they are most effective when taken 30–60 minutes before a meal, preferably before breakfast.^{9,25} Self-treatment should be limited to 14 days, and frequency of use should be no greater than once every 4 months. If heartburn continues during treatment with a nonprescription PPI, persists for more than 2 weeks, or recurs within 4 months, a medical evaluation is recommended.

Adverse effects with short-term use of PPIs are uncommon and may include headache, abdominal pain, diarrhea, constipation, or flatulence. Rare cases of acute interstitial nephritis and subacute cutaneous lupus erythematosus have been reported within weeks or months of initiation of PPI therapy.²¹ PPIs may increase the risk of infectious traveler's diarrhea by decreasing gastric acid and potentially altering gut flora.²¹ Travelers to high-risk areas should discuss the risks and benefits of continuing PPI use with a knowledgeable health care provider before the planned trip. The use of PPIs also has been linked to

increased risk of *Clostridioides difficile* infection, although the overall quality of evidence for this potential adverse effect is low.^{21,26} An increased risk of *C. difficile* infection with proper use of nonprescription PPIs is unlikely, but caution is warranted in high-risk scenarios such as a history of *C. difficile* infection and/or concomitant treatment with broad-spectrum antibiotics.²¹ Patients in whom PPI use is accompanied by severe diarrhea or symptoms of gastroenteritis should stop taking the drug and seek medical evaluation. Patients with ascites secondary to cirrhosis should consult a health care provider before using PPIs owing to the slightly increased associated risk for spontaneous bacterial peritonitis.²¹ Other potential PPI safety concerns that have emerged are unlikely to arise with proper use of nonprescription PPIs, including hypomagnesemia, vitamin B₁₂ deficiency, reduced bone mineral density, cardiovascular events, community-acquired pneumonia, chronic kidney disease, and dementia.²¹ **Table 13–5** lists important drug–drug interactions with PPIs.

Bismuth Subsalicylate

Bismuth subsalicylate (BSS) is indicated for heartburn, upset stomach, indigestion, nausea, and diarrhea. FDA has tentatively determined that BSS is safe and effective for the relief of upset stomach associated with belching and for gas associated with overindulgence in food and drink.²⁷ The mechanism by which BSS relieves heartburn has not been established, but for upset stomach, it is believed to have a topical effect on the stomach mucosa. When this agent is used to treat acid-related symptoms, the adult dose of BSS is 262–525 mg every 30–60 minutes as needed (**Table 13–4**). BSS generally is not recommended for children and should be avoided in patients with salicylate sensitivities or bleeding risks. Because of the risk of Reye syndrome, children and teenagers who have or are recovering from chickenpox or influenza-like symptoms should not use BSS. (For a complete discussion of salicylate risk in children, see **Chapter 5**.) Periodically, some nonprescription products are reformulated to contain BSS in place of an antacid, or vice versa. It is therefore important for patients and health care providers to review product ingredients before initiation of self-treatment to avoid potential complications. Patients taking bismuth salts should be made aware that bismuth may cause the stool and tongue to turn black. Dark-colored stools may be interpreted as a GI bleed, prompting needless medical procedures. (For a complete discussion of BSS, see **Chapter 16**.)

Product Selection Guidelines

Special Populations

Careful consideration of potential risks specific to the geriatric population is indicated before self-treatment for heartburn or dyspepsia can be recommended. Older patients are more likely to take medications that can contribute to heartburn and dyspepsia. They also are at higher risk for developing complications and may have a more severe underlying disorder despite presenting with mild symptoms. A careful assessment to identify potentially problematic medications and exclusions to self-treatment should be performed. If self-treatment is appropriate, potential drug–drug interactions and renal function should be considered in developing recommendations for nonprescription medications. Aluminum- or magnesium-containing antacids should be used sparingly, if at all, in patients with decreased renal function; if an H2RA is appropriate, the lower dose should be selected. Cimetidine should be avoided because of associated increased risks for adverse effects and drug–drug interactions. Omeprazole, esomeprazole, and lansoprazole may be used in patients with renal impairment. Sodium bicarbonate should be avoided in patients with sodium-sensitive comorbidity. The 2019 updated American Geriatrics Society (AGS) Beers Criteria for Potentially Inappropriate Medication (PIM) Use in Older Adults recommend avoiding H2RAs in geriatric patients with or at high risk for delirium, owing to their potential for inducing or worsening delirium.²⁸ A short course of a PPI, consistent with nonprescription labeling, is acceptable.

In children older than 2 years with mild, transient, and infrequent heartburn, acid indigestion, or sour stomach, children's formulas of calcium carbonate-containing antacids may be tried. Lifestyle modifications as discussed in the “Nonpharmacologic Therapy” section also should be recommended. If symptoms are frequent or not responsive to treatment, the child should be referred to an appropriate health care provider for further evaluation.²⁹ If antacids are recommended, an assessment of the child's average daily intake of calcium may help guide the recommendation. The recommended daily intake of calcium for children 2–3 years of age is 700 mg, 4–8 years is 1000 mg, and 9–18 years is 1300 mg.¹⁷ Nonprescription H2RAs are labeled for patients 12 years of age and older, and nonprescription PPIs are indicated for patients 18 years of age or older.

Infrequent and mild heartburn in pregnant women should be treated initially with dietary and lifestyle modifications.³⁰ Calcium- and magnesium-containing antacids may be used safely if the recommended daily dosages are not exceeded. Special attention should be given to the recommended intake of calcium during pregnancy (1000–1300 mg/day).¹⁷ If the pregnant woman's diet already meets this recommendation, the addition of a calcium-containing antacid may cause her to exceed the upper limit of 2500 mg of calcium per day. H2RAs are considered to be compatible with pregnancy. Data are limited but indicate no increased risk of congenital malformations.³¹ Data on use of PPIs during pregnancy are limited. Epidemiologic studies of omeprazole do not demonstrate increased risk of major congenital malformations or other adverse pregnancy outcomes with first-trimester use.^{32,33} The risk associated with lansoprazole also appears to be low.^{31,34} Human data on the safety of esomeprazole in pregnancy are lacking, but no teratogenicity was noted in animal reproduction studies.³³ A meta-analysis of observational studies of H2RA or PPI use during pregnancy suggested an association with increased risk of childhood asthma.³⁵ (See the Preface for a detailed explanation of pregnancy data.) Pregnant women with frequent or moderate to severe heartburn should be referred for medical evaluation.

Aluminum-, calcium-, or magnesium-containing antacids are considered safe in women who are breastfeeding.³⁶ The American Academy of Pediatrics considers cimetidine to be compatible with breastfeeding. However, famotidine is less concentrated in breast milk and may be preferable to cimetidine or ranitidine.³¹ Limited data indicate that low levels of omeprazole and esomeprazole appear in breast milk.^{33,37,38} The amount an exclusively breastfed infant would receive is well below the usual dose of these medications used to treat neonates.^{37,38} There is no information regarding the use of lansoprazole during lactation.³⁴

Patient Factors

Medication selection should be based on the patient's reported frequency, duration, and severity of symptoms; the cost of the medication; potential drug–drug interactions and adverse effects; and the patient's preference. The adverse effect profile is especially important in the selection of antacids. For example, if a patient has a tendency toward constipation, a less constipating antacid, such as magnesium hydroxide, would be more appropriate, and constipating antacids, such as calcium carbonate, should be avoided.

Patient Preferences

Antacids and antisecretory drugs are available in a wide range of prices, flavors, and dosage forms. Once the most appropriate nonprescription medication is determined, the patient should be involved in picking a product that is affordable, palatable, and practical to administer. Presence of inactive ingredients such as dyes, sodium, and sugar should be considered in selection of medications for patients with allergies, sensitivities, certain medical conditions, or dietary restrictions.

Complementary Therapies

Acupuncture may reduce reflux and improve GERD-related symptoms as well as dyspepsia.^{39,40} Limited data suggest that melatonin may be effective for reducing reflux and improving GERD-related symptoms.^{39,41} A blend of 9 botanicals (STW5 [Iberogast]) has been used in Germany for more than 50 years. Clinical trials support its use for symptom reduction in patients with dyspepsia and acid regurgitation.^{39,40,42} Rikkunshito, a traditional Japanese herbal medicine, reduces abdominal pain, heartburn, and abdominal distention in patients with functional dyspepsia.⁴⁰ A peppermint oil–caraway oil combination product also significantly relieved symptoms of dyspepsia compared with placebo.⁴⁰ Of note, these complementary and alternative agents and modalities are used chronically, not as needed. They may have a role in the treatment of patients diagnosed with GERD or functional dyspepsia. There is no evidence for as-needed use of botanicals in managing intermittent heartburn or dyspepsia. (See [Chapter 51](#) for a more thorough discussion of natural products.)

Assessment of Heartburn and Dyspepsia: A Case-Based Approach

Cases 13–1 and 13–2 illustrate the assessment of two different patients presenting with heartburn and dyspepsia.

Case 13–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient complains of recurring substernal burning sensation after eating large meals. It occurs 3 times per week. The discomfort is rated a 5 on a scale of 1-10 and is associated with a feeling of fullness and occasional hiccups. Symptoms typically last 3-4 hours after eating.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Symptoms occur after eating dinner and often are associated with large meals, especially when eating out with her friends, which she does 2-3 times per week.
c. Description of the patient's efforts to relieve the symptoms	Patient has tried Tums Extra Strength (calcium carbonate 750 mg) after meals approximately 3 times per week to help relieve the symptoms. It works sometimes but wears off within an hour. She also does not like the chalky taste.
d. Patient's identity	Denise Johnson
e. Patient's age, gender, height, and weight	39 years, female, 5'2", 150 lb
f. Patient's occupation	Elementary school teacher of English as a second language
g. Patient's dietary habits	Normal balanced diet; drinks one cup of coffee every morning; drinks two glasses of wine per week with her friends.
h. Patient's sleep habits	Sleeps 6-8 hours per night.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	<i>Hypertension:</i> lisinopril 10 mg daily <i>Depression:</i> escitalopram 20 mg daily <i>Pain:</i> ibuprofen 200 mg as needed for headaches and muscle or joint pain
j. Allergies	Penicillin

Relevant Evaluation Criteria	Scenario/Model Outcome
k. History of other adverse reactions to medications	None
l. Other (describe) _____	
Assess	
2. Differentiate patient's signs/symptoms and correctly identify the patient's primary problem(s).	Moderate frequent postprandial substernal burning more than twice per week is consistent with heartburn.
3. Identify exclusions for self-treatment.	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer Ms. Johnson to her primary care provider. (2) Recommend lifestyle modifications. (3) Recommend discontinuation of NSAID use. (4) Recommend a nonprescription acid-reducing product. (5) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	A nonprescription acid-reducing product should provide relief of symptoms for the desired duration, without undesirable adverse effects. A PPI would be appropriate because Ms. Johnson's symptoms occur more often than 2 times per week. She should stop NSAID use and consider lifestyle modifications.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Take esomeprazole 20 mg 30 minutes before your morning meal every day for 14 days. Lifestyle changes also can help manage symptoms."
7. Explain to the patient or caregiver the rationale for selecting	"Because you are experiencing moderate but frequent heartburn, a PPI such as esomeprazole may work best."

Relevant Evaluation Criteria	Scenario/Model Outcome
the recommended therapeutic approach from the considered therapeutic alternatives.	Other heartburn medications may not provide complete relief. Seeing a primary care provider may not be necessary if you obtain adequate relief and your symptoms do not become more severe or frequent.”
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
Solicit follow-up questions from the patient or caregiver.	“Is there anything else that I can do to help with my symptoms besides taking a medication?”
Answer the patient’s or caregiver’s questions.	“You can try to cut out coffee and alcohol from your diet and also try to eat smaller portions when you go out to dinner with your friends. Additionally, weight loss may help to relieve symptoms.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Ask Ms. Johnson to update you by phone or text on her response to the esomeprazole, or call the patient in 1 week to evaluate her response.
Key: H2RA = Histamine type 2 receptor antagonist; NSAID = nonsteroidal anti-inflammatory drug.	

Case 13–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	

Relevant Evaluation Criteria	Scenario/Model Outcome
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient suffers from ongoing upper abdominal discomfort. Patient describes a chronic cough that persisted when his lisinopril was stopped 3 months ago and a burning pain that fluctuates throughout the day. Pain severity varies at 2-4 on a scale of 1-10. Symptoms started about 6 months ago.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Eating a large meal and having a beer tend to make it worse.
c. Description of the patient's efforts to relieve the symptoms	Patient has tried esomeprazole 20 mg daily for 2 weeks with some relief.
d. Patient's identity	Peter Payne
e. Patient's age, gender, height, and weight	58 years, male, 6'2", 220 lb
f. Patient's occupation	Banker
g. Patient's dietary habits	Normal balanced diet; drinks 2 cups of coffee every day; occasional alcohol consumption.
h. Patient's sleep habits	Sleeps 5-6 hours per night.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	<i>Hypertension:</i> irbesartan 150 mg daily <i>Diabetes:</i> metformin 500 mg twice daily <i>Hyperlipidemia:</i> rosuvastatin 10 mg daily <i>General health:</i> multivitamin daily <i>Hypertension:</i> irbesartan 150 mg daily
j. Allergies	NKDA
k. History of other adverse reactions to medications	None
l. Other (describe) _____	

Relevant Evaluation Criteria	Scenario/Model Outcome
Assess	
2. Differentiate patient's signs/symptoms and correctly identify the patient's primary problem(s).	Late-onset and ongoing GI symptoms; chronic cough. Not consistent with uncomplicated heartburn or uncomplicated dyspepsia.
3. Identify exclusions for self-treatment.	Symptom onset after age 45, chronic cough, and lack of improvement after completing a course of a nonprescription PPI indicate need for medical referral.
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	(1) Refer Mr. Payne to an appropriate health care provider for medical evaluation. (2) Recommend a nonprescription product with lifestyle modifications. (3) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Refer Mr. Payne to an appropriate health care provider for a differential diagnosis.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Call your primary care provider for a medical evaluation."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"You need to see your primary care provider, as your symptoms may indicate a more serious medical condition that needs to be evaluated. Further treatment with a nonprescription medication is not appropriate."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient	Criterion does not apply in this case.

Relevant Evaluation Criteria	Scenario/Model Outcome
or caregiver.	
Solicit follow-up questions from the patient or caregiver.	“Why can’t I take more of the esomeprazole since it helped somewhat before?”
Answer the patient’s or caregiver’s questions.	“Esomeprazole is approved to be used as a nonprescription product for only 2 weeks; after that, if no improvement occurs, further evaluation is needed.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Mr. Payne in 1-2 days to ensure that he has contacted his primary care provider for an appointment.

Key: NKDA = No known drug allergies; PPI = proton pump inhibitor.

Patient Counseling for Heartburn and Dyspepsia

Many cases of uncomplicated heartburn and dyspepsia are self-treatable. For optimal outcomes, patients need to understand how to treat symptoms appropriately and when to seek additional care. This information is provided in the box “Patient Education for Heartburn and Dyspepsia” To avoid duplication of therapies, patients should be advised to avoid taking nonprescription antacids, H2RAs, or PPIs with a prescription H2RA or PPI.

Evaluation of Patient Outcomes for Heartburn and Dyspepsia

Patients with infrequent heartburn and dyspepsia should obtain symptomatic

relief within 5 minutes when treated with an antacid or within 30–45 minutes when treated with an H2RA. Patients taking PPIs may require up to 4 days for complete relief of symptoms, but most patients are asymptomatic within 1–2 days. Self-treating patients should be encouraged to contact their primary care provider or pharmacist to report the effectiveness of therapy and any problems that arise during treatment (e.g., adverse effects). In some cases, the provider may make a follow-up contact to assess therapeutic outcomes. If the patient reports an inadequate response to therapy, increased frequency of symptoms, or new symptoms, reevaluation is indicated to determine whether a different therapy is suitable or whether medical referral is necessary. Adverse effects may be managed by adjusting the dose or switching to another product. Patients in whom atypical or alarm symptoms ([Figure 13–2](#)) develop should be referred to their primary care provider for further evaluation.

Patient Education for Heartburn and Dyspepsia

Heartburn and dyspepsia (indigestion) are often self-treatable conditions. Heartburn is characterized by a burning sensation in the chest, usually occurring after meals. Dyspepsia is characterized by discomfort in the upper abdomen. The goals of self-treatment are (1) to provide complete relief of symptoms, (2) to reduce recurrence of symptoms, and (3) to prevent and manage unwanted effects of medications.

Nondrug Measures

- Avoid food, beverages, and activities that may precipitate or increase the frequency and severity of symptoms.
- If possible, avoid the use of medications that may aggravate heartburn or dyspepsia.
- Avoid eating large meals.
- Stop smoking.
- Lose weight if overweight and not pregnant.
- Reduce intake of dietary fat.
- If nocturnal symptoms are present:

- Avoid lying down within 2–3 hours of a meal.
- Elevate the head of the bed using 6- to 8-inch blocks, or use a foam pillow wedge under the upper body.
- Lie on your left side.

Nonprescription Medications

- Store all medications at 68°–77°F (20°–25°C), and protect them from heat, humidity, and moisture. Discard after expiration date.

Antacids

- Antacids (sodium bicarbonate, calcium carbonate, magnesium hydroxide, and aluminum hydroxide) are available alone and in combination with each other and other ingredients.
- Antacids work by neutralizing acid in the stomach.
- Antacids may be used for relief of mild, infrequent heartburn or dyspepsia (indigestion).
- Antacids usually are taken at the onset of symptoms. Relief of symptoms typically begins within 5 minutes.
- Because antacids come in a variety of strengths and concentrations, it is essential to consult the label of an individual product for the correct dose and frequency of administration. Generally antacids should not be used more than 4 times a day, or regularly for more than 2 weeks.
- If symptoms are not relieved with recommended dosages, consult a health care provider.
- Diarrhea may occur with magnesium- or magnesium/aluminum-containing antacids; constipation may occur with aluminum- or calcium-containing antacids. Discontinue use if these effects are troublesome or do not resolve in a few days.
- In children older than 2 years, mild transient and infrequent heartburn, acid indigestion, or sour stomach may be treated with children's products containing calcium carbonate if they are used according to package directions.
- Pregnant women with mild and infrequent heartburn may use calcium- and magnesium-containing antacids safely if

recommended daily dosages are not exceeded.

- Patients with kidney dysfunction should consult their primary care provider before self-treatment with antacids.
- Patients taking tetracyclines, fluoroquinolones, azithromycin, ketoconazole, itraconazole, iron supplements, or levothyroxine should not take antacids with these medications. (See [Table 13–5](#) for specific information on drug–drug interactions with antacids.)

Histamine Type 2 Receptor Antagonists (H2RAs)

- H2RAs—cimetidine, famotidine, and ranitidine—may be used to relieve symptoms of or prevent heartburn and indigestion associated with meals.
- H2RAs work by decreasing acid production in the stomach.
- H2RAs usually are taken at the onset of symptoms or 30–60 minutes before symptoms are expected. Relief of symptoms can be expected to begin within 30–45 minutes after the medication is taken. A combination product that contains both an antacid and an H2RA provides faster relief of symptoms.
- H2RAs generally relieve symptoms for 4–10 hours.
- H2RAs can be taken when needed, up to twice daily for 2 weeks.
- H2RAs should be used for relief of mild to moderate, infrequent, and episodic heartburn and indigestion when a more prolonged effect is needed. Use lower dosages for mild heartburn and higher dosages for moderate symptoms.
- Adverse effects are uncommon but may include headache, diarrhea, constipation, dizziness, or drowsiness. If any of these effects occurs, stop use and consult a health care provider for an alternative product.
- Cimetidine may interact with many medications. Consult a health care provider if you also are taking theophylline, amiodarone, warfarin, clopidogrel, ketoconazole, phenytoin, or other medications.

Proton Pump Inhibitors (PPIs)

- Nonprescription PPIs are indicated for mild to moderate frequent

heartburn that occurs 2 or more days a week. These drugs are not intended for the relief of mild, occasional heartburn.

- PPIs—omeprazole, esomeprazole, and lansoprazole—work by decreasing acid production in the stomach.
- PPIs should be taken with a glass of water every morning 30–60 minutes before breakfast for 14 days. Make sure to take the full 14-day course of treatment.
- Do not take more than 1 tablet a day. If a dose is missed, take as soon as possible within 12 hours; if it has been more than 12 hours, then skip that dose and resume with next scheduled dose.
- Complete resolution of symptoms should be noted within 4 days of initiating treatment.
- If symptoms persist, worsen, are not adequately relieved after 2 weeks of treatment, or recur before 4 months has elapsed since treatment, consult your primary care provider.
- Do not crush or chew tablets or capsules because this may decrease the effectiveness of the PPI.
- Adverse effects are uncommon but may include headache, abdominal pain, diarrhea, constipation, or gas. If these effects occur, stop use and consult a health care provider for an alternative product.
- Consult a health care provider if you also are taking warfarin, clopidogrel, cilostazol, ketoconazole, diazepam, antiretroviral medications, methotrexate, theophylline, tacrolimus, mycophenolate mofetil, digoxin, or other medications.

When to Seek Medical Attention

- Consult your primary care provider if you experience any of the following:
 - Heartburn or dyspepsia (indigestion) that lasts longer than 3 months
 - Heartburn or dyspepsia (indigestion) that occurs with recommended dosages of nonprescription medications
 - Heartburn or dyspepsia (indigestion) that still occurs after 2 weeks of continuous treatment with a nonprescription medication

- Heartburn that awakens you during the night
- Difficulty or pain on swallowing foods
- Black tarry feces or vomiting of blood or black material
- Chest pain or shoulder, arm, or neck pain, with shortness of breath
- Chronic hoarseness, cough, choking, or wheezing
- Unexplained weight loss
- Continuous nausea, vomiting, or diarrhea
- Severe stomach pain
- Occurrence of troublesome side effects that do not resolve on discontinuing the nonprescription medication

Key Points for Heartburn and Dyspepsia

- Self-treatment of heartburn and dyspepsia should be limited to mild or moderate symptoms, including postprandial burning in the upper abdomen and centralized abdominal discomfort.
- Patients with atypical or alarm symptoms ([Figure 13–2](#)) should be referred for further evaluation.
- In children older than 2 years, treatment of mild transient and infrequent heartburn, acid indigestion, or sour stomach symptoms should be limited. Prompt referral should be made if symptoms are frequent or persist despite treatment.
- Pregnant women may self-treat for mild and infrequent heartburn with calcium- and magnesium-containing antacids.
- Patients with heartburn should be counseled on nondrug measures, such as the dietary and lifestyle modifications listed in the box “Patient Education for Heartburn and Dyspepsia.”
- Self-treating patients should be advised about the advantages and disadvantages of various antacids and acid-reducing

products so that they can select a product that is best suited to their needs.

- Antacids provide temporary relief for mild and infrequent heartburn and dyspepsia. Dosages are product-specific because of variability in antacid ingredients and concentrations.
- H2RAs are indicated for infrequent, mild to moderate heartburn or dyspepsia. They may be taken at the onset of symptoms or 30–60 minutes before an event (e.g., meal, exercise) that may cause symptoms.
- PPIs are indicated for treatment of frequent heartburn (occurring ≥ 2 days a week) and should be used for a maximum of 14 consecutive days, no more frequently than every 4 months. They are not intended for immediate relief or infrequent symptoms.
- Patients with self-treatable symptoms should be advised to contact their primary care provider if symptoms worsen or if frequent symptoms persist after 14 days of self-treatment.

Chapter 14: Intestinal Gas

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Intestinal gas–related symptoms and conditions that predispose affected patients to intestinal gas formation are common and may be associated with considerable discomfort and lifestyle impairment. The most frequent clinical manifestations are *eructation* (belching of swallowed air), *bloating* (uncomfortable fullness, often with abdominal distention, particularly after eating), and *flatulence* (excessive passage of air from the stomach or intestines through the anus). Differentiation of temporary symptoms from a chronic gastrointestinal (GI) disorder or condition such as irritable bowel syndrome (IBS), lactose intolerance, or celiac disease is important in recommending appropriate nonprescription treatment.

The primary categories of nonprescription pharmacologic agents for intestinal gas are antiflatulence medications (simethicone, activated charcoal), digestive enzymes (lactase replacement and α -galactosidase products), and probiotic products (containing *Bifidobacterium*, *Lactobacillus*, *Saccharomyces*, or *Streptococcus thermophilus* or other species, alone or in combination).

A significant proportion of the U.S. population is affected by conditions that may be associated with intestinal gas symptoms. Intestinal gas can be caused by lactose malabsorption (affecting 29% of the population), IBS (5%–15%), and other, less common medical conditions such as celiac disease (1%–3% of the general population and 10% of first-degree relatives of persons with celiac disease) and pancreatic insufficiency (<1%).^{1–5}

Pathophysiology of Intestinal Gas

Healthy persons and patients who complain of distention carry a volume of approximately 200 mL of gas in the intestinal tract in both the fasting and postprandial states.^{6–8} The composition of intestinal gas is primarily nitrogen (N_2), oxygen (O_2), carbon dioxide (CO_2), hydrogen (H_2), and methane (CH_4).⁶ Increased intestinal gas may be attributable to excessive aerophagia (air swallowing), increased intraluminal production within the bowel, decreased gas absorption due to obstruction, or expansion of intraluminal gas related to

atmospheric pressure changes.

Aerophagia is a major etiologic mechanism for accumulation of intestinal gas (primarily as O₂ and N₂). Contributory factors include eating quickly or gulping beverages, consuming carbonated beverages, anxiety, gum chewing, and smoking.⁹

Diet, underlying medical conditions, genetics, alterations in intestinal flora, and drugs may precipitate or aggravate symptoms attributable to intestinal gas.

Certain foods can increase intestinal gas production, leading to bothersome symptoms.^{10,11} Dietary sugars may be incompletely absorbed in the healthy human small intestine. These sugars are the principal substrates for H₂ gas production in the colon. Similarly, malabsorption may be a problem with other foods, including fatty foods; foods rich in complex carbohydrates; and indigestible oligosaccharides. These substances remain in the intestinal lumen and are passed into the colon, where they provide a substrate for bacterial fermentation and colonic production of H₂, CO₂, and CH₄.⁵ Bacterial fermentation in the small intestine resulting from bacterial overgrowth may lead to production of excessive amounts of intestinal gas. Fermentation in the colon is the primary process for generating intestinal gas and is influenced by the type and quantity of foods ingested (Tables 14–1 and 14–2).

Table 14–1 Gas-Producing Foods

Foods Associated With Minimal Gas Production

- Meats: fowl, fish
- Vegetables: lettuce, peppers, avocado, tomato, asparagus, zucchini, okra, olives
- Fruit: cantaloupe, grapes, berries, fruit juice
- Carbohydrates: refined white sugar and refined white flour
- Other: all nuts, eggs, gelatin

Foods Associated With Moderate Gas Production

- Fruits: citrus, apples
- Carbohydrates: refined white sugar and refined white flour

Foods Associated With Major Gas Production

- Vegetables: onions, celery, carrots, brussels sprouts, cucumbers, cabbage, cauliflower,

- radishes, leeks, parsnips, peas, leafy greens such as kale, beans, potatoes, eggplant
- Fruit: raisins, bananas, apricots, prunes, dried fruit
- Carbohydrates: whole grains, wheat germ, bran, brown rice
- Dairy products: milk, ice cream, cheese (in patients who have trouble digesting lactose; check food labels of processed foods for added lactose or milk-derived ingredients)
- Other: carbonated beverages

Source: [References 7](#) and [8](#).

Table 14–2 Oligosaccharide-Containing Foods Associated With Intestinal Gas Production With Potential Treatment Benefit From α -Galactosidase

Vegetables

Beets

Broccoli

Brussels sprouts

Cabbage

Cauliflower

Corn

Cucumbers

Leeks

Lettuce

Onions

Parsley

Peppers, sweet

Beans

Black-eyed peas

Buckbeans

Broad beans
Chickpeas
Lentils
Lima beans
Mung beans
Pinto beans
Red kidney beans
Grains
Barley
Oat bran
Rice bran
Rye
Sorghum grain
Wheat bran
Whole wheat flour
Other
Soy products (soy milk, tofu)
Seed flour (sesame, sunflower)

Source: [References 7](#) and [8](#).

High-fiber diets may lead to bloating and flatulence. Soluble fiber absorbs water and stabilizes intestinal contractions; however, its supplementation does not appear to decrease GI symptoms.¹² Patients who experience adverse GI effects (bloating, flatulence) from natural fiber preparations (e.g., psyllium) may prefer a soluble semisynthetic fiber supplement (e.g., calcium

polycarbophil).¹²

The odor attributable to flatulence may be worsened by the ingestion of sulfate-containing foods, such as cruciferous vegetables (e.g., broccoli, cabbage); breads and beers containing sulfate additives; and proteins with a high content of the sulfur-containing amino acids methionine and cysteine (e.g., eggs, macadamia nuts, peanuts, pistachio nuts, red meats). Sulfur-based gases (e.g., hydrogen sulfide [H₂S]), methanethiol, and dimethyl sulfide are produced through the action of sulfate-reducing bacteria.¹³ Rating foods by their potential to cause intestinal gas symptoms is difficult, but clinical experience suggests that certain foods are generally more problematic than others (Table 14–1).

Gas-related signs and symptoms may be associated with intake of an excessive amount of air into the upper GI tract with swallowing. Smoking, chewing gum, sucking on hard candies, drinking carbonated beverages, wearing poor-fitting dentures, hyperventilating, or being overly anxious may contribute to swallowing larger-than-normal amounts of air.¹³ Poor eating habits (e.g., “wolfing down” food, gulping beverages) may cause larger amounts of air to enter the stomach.

A number of medical conditions cause or predispose patients to the formation of intestinal gas. Some conditions (e.g., carbohydrate malabsorption, pancreatic insufficiency) lead to production of an increased amount of gas from bacterial fermentation in the colon. The most common cause of carbohydrate malabsorption is lactase deficiency. Lactase is the enzyme that normally breaks down lactose in the intestinal lumen so that it can be absorbed. Physiologic lactase enzyme activity peaks at birth and starts to decline after the first few months of life as infants are slowly weaned from their mother’s milk.

In patients with lactase deficiency, the lactase enzyme is not available in sufficient quantities to break down lactose in dairy products before it reaches the colon. In the colon, the malabsorbed lactose remains in the intestinal lumen, where it is available to colonic bacteria for fermentation to H₂ and other substances. People with lactase deficiency experience GI symptoms (e.g., gas pains, bloating, nausea, diarrhea) on exposure to dairy and other foods containing milk or milk-derived carbohydrates (e.g., caramel).¹⁴ Milk-derived protein (e.g., whey powder, caseinate, other lactoproteins) does not cause lactose-associated GI symptoms unless the product is contaminated with a

milk-derived carbohydrate (i.e., lactose).

Other conditions such as IBS may predispose affected patients to intestinal gas symptoms. Gas pains and bloating are very common in patients with IBS and may be caused by a number of interrelated factors, including heightened sensation of the GI tract to intestinal stretch (i.e., visceral hypersensitivity), altered intestinal motility, activated intestinal immunity, altered brain–gut interaction, and autonomic dysfunction.¹² Small bowel bacterial overgrowth has been proposed as a unifying theory linking these factors, which has stimulated promising research that aims to further define the relationship between intestinal bacterial overgrowth and the onset of IBS symptoms.¹² Probiotic bacteria (e.g., lactobacilli, saccharomycetes, bifidobacteria) are part of the normal “healthy” flora of the intestinal tract. They are thought to maintain intestinal health through a variety of mechanisms, including shifting the intestinal bacterial content in favor of nonpathologic organisms; producing beneficial substances (e.g., short-chain fatty acids); and acting primarily as carbohydrate-fermenting bacteria, thereby reducing symptoms of intestinal gas (see [Chapter 20](#)). Substances such as oligofructose (a “prebiotic”) are used as nutrients by the normal intestinal bacterial flora and by probiotic organisms; with use of prebiotics, however, the normal flora produces greater amounts of CO₂, CH₄, and H₂, which may result in increased symptoms of intestinal gas.^{5,10}

Intestinal gas symptoms may result from other, less common medical conditions such as celiac disease and diabetic gastroparesis. Patients with celiac disease have an intolerance to gluten (a protein present in wheat, rye, barley, and oats). Intestinal gas symptoms may result from the inflammatory response in the GI tract that occurs after exposure to gluten. Once a diagnosis of celiac disease has been made, and after gluten intolerance has been confirmed with accurate testing, affected patients should follow a strict gluten-free diet, preferably under the supervision of an experienced dietitian.¹ The most common sources of gluten are baked goods containing the causative grains (wheat and oat cereals, noodles, and pastas); however, many other food products (especially processed foods containing thickeners) and some medications contain gluten.

A variety of drugs may cause intestinal gas symptoms. These drugs can be categorized broadly by the mechanism of action leading to symptoms caused by physiologic changes:

- Agents that affect intestinal flora (lactulose, antibiotics)

- Drugs that affect metabolism of glucose and other dietary substances (α -glucosidase inhibitors, including acarbose and miglitol; the biguanides, including metformin); and GI lipase inhibitors, such as orlistat
 - Drugs that affect GI motility (narcotics, anticholinergics, calcium channel blockers), including agents that are high in fiber (psyllium) and nonabsorbable polymers (cholestyramine)
 - Products that contain or release gas (effervescent solutions such as Alka-Seltzer)
-

Clinical Presentation of Intestinal Gas

The most frequent clinical manifestations of increased intestinal gas are eructation (belching or burping), bloating and abdominal distention, abdominal discomfort or cramping, and flatulence. Less common signs and symptoms include nausea, borborygmi (audible bowel sounds), and dyspepsia or indigestion.

Eructation is defined as an audible escape of air from the esophagus into the pharynx that can be either involuntary or voluntary. It is classified into two types: supragastric belching and gastric belching. Supragastric belching occurs with air swallowing and release before reaching the stomach. Gastric belching results from escape of air from the esophagus during times of lower esophageal sphincter relaxation. Gastric belching typically is involuntary and commonly occurs 25–30 times per day. Some people experience excessive belching, which may be annoying or embarrassing because of its frequency, intensity, and/or unexpected occurrence.

Gas pains often are described as a generalized, crampy discomfort associated with gaseousness. Passing gas or having a bowel movement may relieve gas pains. In some patients, symptoms may be brought on by stress or anxiety. In others, the size of a meal may affect onset and severity of gas pains, with larger meals causing more bothersome symptoms. Patients who complain of recurrent gas pains (occurring at least 3 days per month in a 3-month period) that are associated with either diarrhea or constipation may have IBS.⁴

Bloating may be characterized as a sensation of tension or fullness in the abdominal area after eating or as a subjective perception that the abdomen is

larger than normal. Patients with bloating may observe that clothes fit more tightly or are uncomfortable to wear. Patients with diabetes who complain that their bloating symptoms are accompanied by a sensation of early satiety or fullness after the ingestion of only a small amount of food may be experiencing diabetic gastroparesis and should be referred to their primary care provider.

Flatulence, or the uncontrollable or frequent passage of typically odiferous intestinal gas through the anus, is normal, although socially taboo in most settings, and occurs either consciously or unconsciously 10–20 times per day, even during sleep.

Algorithm: Intestinal Gas Symptoms

Figure 14–1 Self-care for intestinal gas symptoms. Key: GI = Gastrointestinal; OTC = over-the-counter.

Treatment for Intestinal Gas

Treatment Goals

The goals of therapy are (1) to reduce the frequency, intensity, and duration of intestinal gas symptoms and (2) to reduce the impact of intestinal gas symptoms on the affected person's lifestyle. Because intestinal gas production is normal and necessary for GI tract function, the complete elimination of intestinal gas is not a realistic or attainable goal.

Treatment Approach

Self-treatment for intestinal gas symptoms should begin with an assessment of the patient's history and severity of symptoms, diet, eating habits, medication use, and relevant medical conditions. Most patients will be able to control their symptoms if they understand the basis for these symptoms, follow steps to reduce predisposing factors, and make informed decisions regarding the use of nonprescription medications. Identification of the

underlying cause of intestinal gas will guide treatment decisions for both the patient and the health care provider (Figure 14–1). Inquiry into the patient's diet (including a review of eating habits and the frequency, amount, and type of food and beverages ingested) often can lead to non-drug therapy-based suggestions for controlling the problem. Symptoms that are related to eating habits or diet often will subside quickly once the source of the problem is identified and the necessary changes are made.

Patients for whom symptoms are associated with ingestion of foods containing lactose or oligosaccharides and who have no exclusions for self-treatment (Figure 14–1) may use digestive enzymes (e.g., lactase replacement or α -galactosidase products). The primary categories of nonprescription pharmacologic agents for control of intestinal gas symptoms are antifatulence medications (simethicone, activated charcoal), digestive enzymes (lactase replacement and α -galactosidase products), and probiotic products (e.g., *Bifidobacterium*, *Lactobacillus*, *Saccharomyces*, *Streptococcus thermophilus*, and other species). Although several nonprescription antifatulence products are available (e.g., activated charcoal, simethicone), their use is largely empirical, and evidence supporting a beneficial effect is limited.

Probiotics (see Chapter 20) maintain GI tract health by protecting against pathologic GI flora; they may be useful in some patients to relieve intestinal gas complaints.¹⁶ No consensus has emerged on whether probiotics or prebiotics are beneficial in patients with lactose intolerance or chronic abdominal bloating. Increasing evidence, however, suggests that probiotics may be beneficial for treatment of intestinal gas symptoms in patients with IBS because these agents have favorable effects on the bacterial content of the small intestine and colon.^{15,16} The benefit of probiotics may potentially be linked to specific bacterial strains. More research is needed to identify the true value of individual probiotic products.

Referral for medical evaluation is indicated if any of the exclusion criteria for self-management are present (Figure 14–1). Because gas pains can mimic symptoms of other conditions (e.g., biliary colic and other diseases of the gallbladder and biliary tract, diabetic gastroparesis, peptic ulcer disease, intestinal obstruction, neoplastic disease, pancreatic insufficiency, heart disease), referral to a primary care provider is indicated if the patient is experiencing new-onset, persistent, or frequent and/or severe symptoms. Owing to an increased risk of colorectal cancer after the age of 40 years,

complaints of new or recurrent gas pains constitute a specific age-related risk factor that warrants further medical evaluation.

Patients with diabetes who complain that their bloating symptoms are accompanied by a sensation of early satiety or fullness after the ingestion of only a small amount of food may be experiencing diabetic gastroparesis and should be referred for further evaluation.

Exclusions for self-treatment ([Figure 14–1](#)) should be ruled out in the initial patient assessment before recommendation of any therapy. Referral to a primary care provider for further evaluation should be considered for patients with exclusions for self-treatment and for patients whose symptoms persist after initiation of simple treatment options (e.g., dietary modification, nonprescription medications).

Nonpharmacologic Therapy

General information for controlling intestinal gas symptoms is provided in [Table 14–3](#).¹⁹ Patients may benefit from changes in eating habits and changes in diet. Reducing the consumption of gas-producing foods ([Tables 14–1](#) and [14–2](#)) may be appropriate, depending on the dietary history. Some people are unable to tolerate gas-producing foods and need to completely avoid such foods. Patients with lactose intolerance either should avoid milk and dairy products or should use lactase replacement products. Low-lactose milk products (e.g., Lactaid Milk, Dairy Ease Milk), fortified soy milk, almond milk, or rice milk products may be used as milk substitutes. Low-lactose milk is a prehydrolyzed milk product (i.e., lactose is already hydrolyzed) and contains the same nutrients as in regular milk, but the product is not entirely lactose-free. Soy milk, almond milk, and rice milk products are lactose-free milk alternatives that are low in fat and may be fortified to include calcium and vitamin D. Similarly, patients who are unable to tolerate foods with a high oligosaccharide content should attempt to reduce consumption of such foods or to remove them from the diet.

Table 14–3 Useful Information to Support Patient Self-Management of Intestinal Gas Symptoms

Eating Habit Suggestions

- Avoid the temptation to rush through a meal. Eat and drink slowly in a calm environment.
- Chew food thoroughly.
- Avoid “washing down” solids with a beverage.
- Avoid gulping and sipping liquids, drinking out of small-mouthed bottles or straws, or drinking from water fountains.
- Eliminate pipe, cigar, and cigarette smoking.
- Avoid chewing gum and sucking hard candy, especially those that contain artificial sweeteners (e.g., sorbitol, mannitol).
- Check dentures for proper fit.
- Attempt to be aware of and avoid deep sighing.
- Do not attempt to induce belching or strain to pass gas.
- Do not overload the stomach at any one meal.

Diet

- Keep a food journal for a few days while tracking intestinal gas symptoms.
- Avoid gas-producing foods ([Table 14–1](#)).
- Avoid foods with air whipped into them (e.g., whipped cream, soufflés, sponge cake, milkshakes).
- Avoid carbonated beverages (e.g., sodas, beer).
- Avoid caffeinated beverages (e.g., coffee, energy drinks).

Medication Use and Lifestyle Habits

- Avoid long-term or frequent intermittent use of medications intended for relief of cold and allergy symptoms (e.g., anticholinergic antihistamines such as brompheniramine, chlorpheniramine, doxylamine, and diphenhydramine).
- Avoid or minimize the use of drugs affecting gastrointestinal motility (narcotics and calcium channel blockers).
- Avoid or minimize the use of drugs affecting glucose metabolism (orlistat; α -glucosidase inhibitors, including acarbose and miglitol; and the biguanides, including metformin).
- Avoid or minimize the use of drugs that affect the intestinal flora (lactulose and antibiotics).
- Avoid or gradually increase intake of new foods or medications that are high in fiber (psyllium).
- Avoid nonabsorbable polymers (cholestyramine).
- Avoid medications that contain or release gas (e.g., Alka-Seltzer).
- Avoid tight-fitting garments, girdles, and belts.
- Do not lie down or sit in a slumped position immediately after eating.
- Develop a regular routine of exercise and rest.

Source: [References 10, 11, and 26](#).

An understanding of common food choices made by people of different cultures, ethnicities, and socioeconomic backgrounds can lead to improved identification of dietary patterns known to contribute to intestinal gas symptoms. This knowledge may allow the health care provider to identify and explain, in a culturally sensitive manner, why problematic gas-forming foods are not appropriate options for a specific patient. Addressing dietary issues with family members may be a better approach for developing healthy eating habits over time, especially for children experiencing intestinal gas symptoms.

Pharmacologic Therapy

Simethicone and activated charcoal may relieve symptoms after intestinal gas has formed. α -Galactosidase and lactase enzymes are taken with foods to prevent gas from forming. Lactase replacement products may be beneficial for reducing frequency and severity of excessive intestinal gas and prevention of diarrhea associated with lactose intolerance. These products are used as digestive aids, allowing people with lactose intolerance to incorporate dairy foods into the diet without experiencing intolerable symptoms. Most lactose maldigesters can tolerate some milk (up to 1 cup at a time), so use of these products should be individualized according to the patient's symptoms.

Simethicone

Simethicone (a mixture of inert silicon polymers) is used as a defoaming agent to relieve gas. Simethicone acts in the stomach and intestine to reduce the surface tension of gas bubbles that are embedded in the mucus of the GI tract. As surface tension changes, the gas bubbles are broken or coalesced, allowing them to be eliminated more easily by belching or passing gas through the anus.

The U.S. Food and Drug Administration (FDA) considers simethicone to be safe and effective as an antifatulence agent. In patients with acute, nonspecific diarrhea, the combination of simethicone with loperamide produced quicker relief from gas-related discomfort than either agent alone.¹⁷ However, simethicone's ability to reduce intestinal gas symptoms for all patients with symptoms is questionable.¹⁸ The use of simethicone on a trial basis may be encouraged, because some patients report benefit. The usual adult and pediatric dosages for simethicone are provided in [Table 14-4](#).

Table 14–4 Dosage Guidelines for Products for Self-Management of Intestinal Gas

Agent	Adults	Children > 12 Years	Children 2 to ≤ 12 Years	Children < 2 Years
Simethicone	40–125 mg orally after meals and at bedtime, as needed	40–125 mg orally 4 times daily after meals and at bedtime, as needed	40–50 mg orally 4 times daily after meals and at bedtime, as needed	20 mg orally 4 times daily, after meals and at bedtime, as needed
Activated charcoal	500–520 mg orally after meals, as needed; may repeat hourly	Specific guidelines not available	Specific guidelines not available	Specific guidelines not available
α-Galactosidase	300–450 units orally per serving of food	Specific guidelines not available	Specific guidelines not available	Specific guidelines not available
Lactase enzyme	3000–18,000 units orally at first bite of food or drink containing lactose	3000–18,000 units orally at first bite of food or drink containing lactose	Specific guidelines not available	Specific guidelines not available
Probiotics	Specific guidelines not available	Specific guidelines not available	Specific guidelines not available	Specific guidelines not available

Many antacid products contain a combination of simethicone and antacids; therefore, patients should follow the label instructions for dosages of these products. Use of both agents often is unnecessary, however, and the efficacy of such combination products has not been well studied. Furthermore, single-ingredient antiflatulence products ([Table 14–5](#)) usually contain a higher concentration of simethicone than that found in combination products. Because simethicone is not absorbed from the GI tract, it has no known systemic adverse effects; its safety has been well documented. Of note, however, simethicone is contraindicated in patients with a known hypersensitivity to simethicone products or with suspected intestinal perforation and obstruction.

Activated Charcoal

Activated charcoal is promoted for relief of intestinal gas; however, it is neither approved nor shown to be effective for this indication.¹⁹ The usual adult dosages for this agent are provided in [Table 14–4](#). The proposed antifatulence properties of activated charcoal are related to the adsorbent effects of the substance and its potential to facilitate the elimination of intestinal gas from the GI tract. Activated charcoal has been purported to be beneficial for the elimination of malodorous, sulfur-based gases.¹⁹ However, activated charcoal has poor palatability. External devices containing activated charcoal are available to reduce the odor of flatus in patients with ostomies (see [Chapter 22](#)).

α-Galactosidase

Another FDA-approved agent available for use as an antifatulent is the enzyme α-galactosidase. This enzyme, which is derived from the *Aspergillus niger* mold, hydrolyzes oligosaccharides into their component parts before they can be metabolized by colonic bacteria. α-Galactosidase products are classified as a food. The usual adult and pediatric dosages for this enzyme preparation are provided in [Table 14–4](#).

Because high-fiber foods contain large amounts of oligosaccharides, α-galactosidase is recommended for prophylaxis against excessive intestinal gas production associated with high-fiber diets or consumption of foods that contain oligosaccharides ([Table 14–2](#)). A randomized, double-blind, placebo-controlled trial of α-galactosidase demonstrated that the agent significantly reduced gas-related symptoms in healthy persons who consume oligosaccharide-containing foods.²⁰

The safety of α-galactosidase remains to be determined. Although this enzyme has been used in food processing for years and is regarded as safe by FDA, the amount contained in available pharmacologic products is much greater than that in processed foods. Because the enzyme produces galactose, it should not be used by patients with *galactosemia* (an inherited metabolic disorder in which galactose accumulates in the blood because of deficiency of an enzyme that catalyzes conversion of galactose into glucose). As noted, α-galactosidase is derived from mold, so allergic reactions are possible in patients allergic to molds.

Lactase Replacement Products

Lactase replacement products are used in patients with lactose intolerance (see [Chapter 16](#)). Lactase enzymes break down lactose, a disaccharide, into the monosaccharides glucose and galactose, which are absorbed. Lactase replacement products should be used in patients with lactose intolerance to aid in the digestion of dairy products. No adverse effects are listed for lactase replacement products. The usual adult dose for lactase enzymes is provided in [Table 14–4](#).

Product Selection Guidelines

Special Populations

Several pediatric formulations of simethicone are indicated for the relief of intestinal gas. These products, which contain simethicone 40 mg per 0.6 mL suspension formulation, often are promoted and used to relieve gas associated with colic. However, simethicone has not been found to be superior to placebo for intestinal gas and/or infantile colic.¹⁸ Although its efficacy is questionable, simethicone is not absorbed from the GI tract, and it is considered safe for use in infants and children. No reports linking simethicone to congenital defects have been published to date.¹⁸ Simethicone is considered to be safe for use by nursing mothers.

Safety and efficacy of α -galactosidase products have not been evaluated in infants. However, a small randomized study in 52 children 4–17 years of age found these products to be safe and effective. A large research study would be needed to confirm this result.²⁰ This product should not be used in pediatric patients younger than 4 years of age but may be safely used in older children. Manufacturers recommend that pregnant or nursing women consult their primary care provider before using α -galactosidase. (Please refer to the Preface for a detailed explanation of the pregnancy data.)

No special population considerations are listed for lactase replacement products. Patients should consult their primary care provider if symptoms continue after using a lactase replacement product, or if symptoms are unusual and seem unrelated to eating dairy products.

Patient Factors

α -Galactosidase and lactase replacement products are used to prevent the onset of symptoms in patients unable to tolerate problematic foods.

Simethicone is recommended for patients with gas-related symptoms who need immediate relief and patients who cannot correlate their symptoms with ingestion of certain foods. Activated charcoal may be an alternative to simethicone for patients with gas symptoms, and it may be beneficial for patients who experience malodorous gas production. Because α -galactosidase produces carbohydrates, patients with galactosemia should avoid its use, and patients with diabetes should consult an appropriate health care provider before initiation of self-treatment. Patients with lactase maldigestion who experience symptoms of lactose intolerance should consider taking lactase replacement products at the time of exposure to dairy products.

Patient Preferences

Most products for self-management of intestinal gas are available in a variety of strengths and dosage forms. A liquid formulation of simethicone is available for infants. (See [Chapter 11](#) under “Special Populations” for FDA requirements for dispensing devices included in liquid nonprescription products.)

Simethicone is available as chewable tablets, softgels, edible filmstrips, and liquid drops. Liquid dosage forms and alternative solid dosage forms are generally more expensive than standard solid oral dosage forms (e.g., tablets, capsules) but may be preferable. Activated charcoal is available in two solid oral dosage forms—tablets and capsules—and in a combination product with simethicone.

α -Galactosidase is available as tablets and as meltaway tablets. No difference in effectiveness between these dosage forms has been found, so the choice of a specific product is left entirely to personal preference and convenience.

Several dosage forms of lactase replacement products are available for patients with lactose intolerance. Some products can be added to milk or dairy products to reduce the amount of lactose in the product, or they can be ingested along with dairy products in an effort to reduce the amount of lactose produced when the food is consumed. Additionally, patients may elect to switch to one of the available milk alternatives (e.g., low-lactose milk, fortified soy milk, almond milk, rice milk).

Complementary Therapies

A variety of probiotic and dietary supplements may be used for GI complaints, including intestinal gas and bloating.¹⁶ The most common formulations for intestinal gas ([Table 14–5](#)) are single-bacterium capsules (e.g., *Bifidobacterium infantis*) and capsules containing multiple bacterial species (e.g., a combination of *Lactobacillus acidophilus*, *Lactobacillus paracasei*, *Lactobacillus rhamnosus*, *Bifidobacterium*, and *Streptococcus thermophilus*). Functional fermented food products with live active cultures of probiotic species (e.g., kombucha tea, kefir products) also are available. In patients with IBS and those with lactose intolerance, limited but increasing evidence suggests that specific probiotics provide temporary relief from GI symptoms.¹⁶ Probiotic bacteria leave the intestine soon after therapy is discontinued. With probiotic therapy, daily administration is required to maintain bacterial populations in the intestinal flora. A trial of 14 days is generally recommended for patients embarking on a probiotic regimen. Research shows that probiotics are effective in reducing the incidence of antibiotic-associated diarrhea. More studies are required to identify the probiotic strains that are most efficacious for patients receiving specific antibiotics.²¹ (For more information on probiotics, see [Chapter 20](#).)

Table 14–5 Selected Nonprescription Antiflatulence Products	
Trade Name	Primary Ingredient(s)
Single-Entity Simethicone Products	
Gas-X Extra Strength Chewable Tablets	Simethicone 125 mg
Gas-X Extra Strength Softgels	Simethicone 125 mg
Mylanta Gas Maximum Strength Chewable Tablets	Simethicone 125 mg
Gas-X Ultra Strength Softgels	Simethicone 180 mg
Little Remedies for Tummys Gas Relief Drops	Simethicone 40 mg/0.6 mL

Trade Name	Primary Ingredient(s)
Activated Charcoal Products	
CharcoCaps Capsules	Activated charcoal 260 mg
α-Galactosidase Replacement Products	
Beano Tablets	α-Galactosidase 400 units (1 tablet)
Beano Meltaways Tablets	α-Galactosidase 450units (1 tablet)
Lactase Replacement Products	
Lactaid Original Strength Caplets	Lactase enzyme 3000 units (1 caplet)
Lactaid Fast Act Caplets	Lactase enzyme 9000 units (1 caplet)
Lactase Fast Act Chewable Tablets	Lactase enzyme 9000 units (1 tablet)
Probiotic Products	
Activia Probiotic Yogurt	<i>Lactobacillus bulgaricus</i> ; <i>Streptococcus thermophilus</i> ; <i>Bifidobacterium animalis</i> DN173010/CNCM I-2494 (1 × 10 ⁸ live bacteria per gram of yogurt)
Align Digestive Care Probiotic Supplement Capsules	<i>Bifidobacterium infantis</i> 35624 (4 mg = 1 × 10 ⁹ live bacteria per capsule)
Culturelle Digestive Health Capsules	<i>Lactobacillus rhamnosus</i> (1 × 10 ¹⁰ live bacteria per capsule)
Culturelle Kids Chewable Tablets	<i>Lactobacillus rhamnosus</i> (5 × 10 ⁹ live bacteria per tablet)
DanActive Probiotic Dairy Drink	<i>Lactobacillus bulgaricus</i> ; <i>Streptococcus thermophilus</i> ; <i>Lactobacillus casei</i> DN-114 001 (1 × 10 ¹⁰ live bacteria per 93 mL)
Florastor	<i>Saccharomyces boulardii</i> (lyophilized) CNCM I-745 freeze-dried capsules 250 mg
Florastor Kids Granules	<i>Saccharomyces boulardii</i> (lyophilized) CNCM I-745 freeze-dried oral granules 250 mg (1 packet)

Herbal carminatives (e.g., fennel seed, Japanese mint, peppermint, spearmint) also are commonly used for self-management of intestinal gas symptoms.²² Despite insufficient evidence, these agents are widely used for self-treatment for intestinal gas and IBS.^{22,23} Carminatives may reduce the tone of the lower esophageal sphincter, so consumption of these preparations should be minimized or avoided by patients with gastroesophageal reflux disease (see [Chapter 13](#)); however, this effect on lower esophageal sphincter tone may be less problematic in healthy persons with intestinal gas symptoms.²⁴ Fennel seed can cause photodermatitis and is contraindicated during pregnancy; moreover, the active herbal principle enters breast milk in lactating women. If fennel seed is used, patients should be advised to avoid excessive sunlight and to cease use during pregnancy and lactation. (Please refer to the Preface for a detailed explanation of the pregnancy data.) In addition, coadministration of fennel with ciprofloxacin may lead to reduced ciprofloxacin levels through a chelation mechanism, so doses should be spaced appropriately in patients using both agents.²⁵

Assessment of Intestinal Gas Complaints: A Case-Based Approach

When a patient complains of intestinal gas symptoms, it is important to try to discern any contributing factors and the duration, severity, and frequency of symptoms ([Table 14–6](#)). Behaviors and products that produce relief may provide clues to the underlying cause. A thorough review to identify dietary habits, existing medical problems, and use of prescription and nonprescription medications is warranted.

Table 14–6 Differentiation of Intestinal Gas Discomfort and Irritable Bowel Syndrome

Criterion	Intestinal Gas Discomfort	Irritable Bowel Syndrome
Location	Generalized discomfort in the upper, mid-, or lower abdomen	Generalized discomfort, bloating, and/or pain in the lower abdomen or colon
Signs	Eructation (upper abdomen): belching of air; bloating (mid-abdomen): increased abdominal	No physical signs of disease; no fever, melena, hematochezia,

Criterion	Intestinal Gas Discomfort	Irritable Bowel Syndrome
	girth; flatulence (lower abdomen, colon): excessive air or other gas in the stomach and intestines	or signs of other gastrointestinal disorders
Symptoms	Sensation of accumulated intestinal gas; may manifest as minimal physical discomfort but with significant negative psychosocial effects	Vary widely but are commonly described as abdominal pain that is relieved after a bowel movement, is accompanied by either diarrhea or constipation, and usually lasts at least 3 months
Onset	May begin at any age	Begins in early adulthood or, rarely, after the age of 60 years
Etiology	Symptoms commonly believed to be caused by an excessive amount of gas in the stomach (leading to eructation) and intestines (with bloating or flatulence); other potential causes: lactase deficiency, overgrowth of intestinal bacteria, and excessive air swallowing (aerophagia)	UnknownMay result from altered gastrointestinal motility, heightened visceral sensitivity, and/or overgrowth of intestinal bacteria
Exacerbating factors	Diet; underlying medical conditions; and certain drugs (e.g., lactulose, antibiotics, α -glucosidase inhibitors, orlistat, narcotics, anticholinergics, calcium channel blockers, psyllium or cholestyramine, effervescent solutions)	Stress; overeating; problem foods (e.g., alcohol, chocolate, caffeinated beverages, dairy products, sugar-free products that contain sorbitol or mannitol); foods high in fat
Modifying factors	Minimization of exacerbating factors	Minimization of exacerbating factors; primary care provider evaluation and treatment

Cases 14–1 and 14–2 are examples of the assessment of two different patients with intestinal gas complaints.

Case 14–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient complains of occasional stomach pain, bloating, and flatulence. She states these symptoms started 4–5 weeks ago and have been progressively getting worse. Symptoms now include nausea and occasional vomiting.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	The patient states that the symptoms seem to be consistently present throughout the day and notes that the pain is sometimes diffuse. She has not been able to identify any cause.
c. Description of the patient's efforts to relieve the symptoms	She has tried simethicone 125 mg 4 times a day to alleviate the gas symptoms. She also has tried to keep a food diary to identify any cause.
d. Patient's identity	Michelle Laster
e. Patient's age, gender, height, and weight	45 years, female, 5 ft 2 in., 185 lb
f. Patient's occupation	Accountant
g. Patient's dietary habits	She follows an intermittent fasting diet and frequently consumes prepackaged meals.
h. Patient's sleep habits	7–8 hours a night
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	<i>Depression:</i> citalopram 40 mg, 1 tablet daily
j. Allergies	No known allergies
k. History of other adverse reactions to medications	None
l. Other	Over the past several months, the patient reports

Relevant Evaluation Criteria	Scenario/Model Outcome
	losing 10 lb without changing her diet or increasing exercise.
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s) (Table 14-6).	Abdominal symptoms are consistent with intolerance to multiple foods, suggesting the presence of lactose intolerance, oligosaccharide intolerance, and possibly gluten sensitivity (celiac disease). Fatigue and weight loss support a disorder with a nutritional deficiency component, possibly IBS.
3. Identify exclusions for self-treatment (Figure 14-1).	Unintended weight loss; presence of symptoms for a prolonged period; increasing severity of symptoms; onset of symptoms after the age of 40 years
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer patient to an appropriate health care provider. (2) Recommend that patient keep a food, stress, and symptom journal. (3) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Ms. Laster should be referred to an appropriate health care provider for a definitive diagnosis.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"You should immediately follow up with your primary care provider or gastroenterologist."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Available over-the-counter treatment will not adequately address the severity of the current symptoms you have. It is important that you follow up with your primary care provider to identify the cause of your complaints and associated weight loss."

Relevant Evaluation Criteria	Scenario/Model Outcome
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	Criterion does not apply in this case.
Solicit follow-up questions from the patient or caregiver.	“Is there anything that I can do right now to address my symptoms before getting in to see the doctor?”
Answer the patient’s or caregiver’s questions.	“You’ve tried all the products I would recommend, and there is really nothing else that would help at this point. Immediately following up with your primary care provider is the best course of action.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Ms. Laster in 1-2 days to ensure that she sought medical care and made an appointment.

Key: IBS = Irritable bowel syndrome.

Case 14–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient’s symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient presents with complaints of bloating, “burping,” and flatulence for the past few weeks. These symptoms are mild but uncomfortable.

Relevant Evaluation Criteria	Scenario/Model Outcome
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Symptoms seem to be worse after large meals. Patient notices less bloating after episodes of burping or flatulence.
c. Description of the patient's efforts to relieve the symptoms	The patient hasn't tried anything yet.
d. Patient's identity	Marco King
e. Patient's age, gender, height, and weight	42 years, male, 6 ft, 260 lb
f. Patient's occupation	Insurance agent
g. Patient's dietary habits	Mr. King states he "loves food," especially Mexican and Italian dishes, and his preferred beverages are soda and sparkling water.
h. Patient's sleep habits	7 hours a night
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	<i>Hyperlipidemia</i> : atorvastatin 40 mg, 1 tablet daily
j. Allergies	No known allergies
k. History of other adverse reactions to medications	None
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s) (Table 14-6).	Patient is currently experiencing intestinal gas and bloating that may be due to dietary choices.
3. Identify exclusions for self-treatment (Figure 14-1).	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to	Options include (1) Refer patient to an appropriate health care

Relevant Evaluation Criteria	Scenario/Model Outcome
determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	provider. (2) Recommend self-care until patient can see an appropriate health care provider. (3) Recommend self-care with antifatulence product. (4) Recommend that patient keep a food journal and decrease intake of problematic foods. (5) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Mr. King should take a simethicone product to address his bloating, "burping," and flatulence. He should also keep a food journal and should be advised to decrease his intake of problematic foods and avoid large meals and carbonated beverages.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Gas-X Extra Strength softgels can be taken with meals or snacks to help with flatulence. You should keep a food journal to identify problematic foods. Avoid eating large meals and drinking carbonated beverages."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"The simethicone in the Gas-X softgels can help expel the gas bubbles formed in your stomach and intestine, which will help with belching, flatulence, or bloating. Keeping a food journal will help you identify problematic foods to avoid. Reducing meal size and intake of carbonated beverages should also help decrease the bloating you have been experiencing."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	

Relevant Evaluation Criteria	Scenario/Model Outcome
a. Appropriate dose and frequency of administration	See Table 14-4 .
b. Maximum number of days the therapy should be employed	No maximum, so long as the symptoms are relieved and do not worsen.
c. Product administration procedures	Take the product by mouth.
d. Expected time to onset of relief	Soon after administration
e. Degree of relief that can be reasonably expected	"The simethicone in the Gas-X softgels should help prevent or reduce your symptoms."
f. Most common adverse effects	None
g. Adverse effects that warrant medical intervention should they occur	None
h. Patient options in the event that condition worsens or persists	See Figure 14-1 .
i. Product storage requirements	Store in a cool, dry place out of children's reach.
Solicit follow-up questions from the patient or caregiver.	"Can I take too much of this product?"
Answer the patient's or caregiver's questions.	"Taking more doses than recommended by the manufacturer will not provide any additional relief. Follow the dosing instructions listed on the package."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Call Mr. King in 1 week to evaluate his symptoms and response to treatment. Make sure you have his current phone number on file.

Key: n/a = Not applicable.

Patient Education for Intestinal Gas

The objectives of self-treatment are (1) to quell the symptoms of intestinal gas and (2) to reduce the chance of recurrence of symptomatic episodes. For most patients, carefully following product instructions and the self-care measures listed below will help ensure optimal therapeutic outcomes.

Nondrug Measures

- If possible, avoid foods known to cause intestinal gas.
- Avoid activities and dietary habits known to introduce gas into the digestive system, such as drinking carbonated beverages.

Nonprescription Medications

- Lactase replacement products and α -galactosidase should be taken with foods to prevent intestinal gas from forming.
- Simethicone is used to treat intestinal gas symptoms after onset.

α -Galactosidase

- Do not cook with α -galactosidase products. Add to food after it has cooled, because food temperatures higher than 130°F (55°C) may inactivate the enzyme.
- With drop-specific formulations, add drops to the first bite of problem foods.
- With tablets, swallow, chew, or crumble the recommended number of tablets for consumption with the first bite of problem foods.
- An average meal may contain three servings of a problem food. If needed, use more tablets for larger meals, up to the maximum recommended dose.

Lactase Replacement Products

- Take at first bite of dairy- or lactose-containing food.
- Dosing may vary according to the amount of lactase in the product

and the level of lactose intolerance.

- Do not take more than the recommended maximum daily dose.
- Low-lactose milk or fortified soy milk products also may be consumed to supplement dietary intake of calcium.

Simethicone

- For infants, to ease administration, mix the suspension with 1 ounce of cool water, infant formula, or other liquid.
- Discontinue simethicone if adequate relief is not obtained within 24 hours.

When to Seek Medical Attention

- Seek medical attention if symptoms do not resolve or if they worsen.

Patient Counseling for Intestinal Gas

Patient counseling is important to ensure the appropriate selection and use of nonprescription medications for self-management of intestinal gas. Patients should be encouraged to keep a food journal in an effort to identify those that are problematic. Avoidance of foods or other substances that cause intestinal gas is the best advice to give patients. The health care provider should explain the proper use of medications for intestinal gas symptoms and should warn the patient about possible adverse effects. The box “Patient Education for Intestinal Gas” contains specific information to include in patient counseling.

Evaluation of Patient Outcomes for Intestinal Gas

Many patients with excessive intestinal gas experience mild to moderate distress, and the discomfort is generally self-limiting, with resolution within 24

hours. Mild to moderate gas symptoms and bloating are managed primarily with diet modification, and some relief may be obtained with nonprescription drug therapy. With effective treatment, the patient can expect reduced intensity and duration of gas-related signs and symptoms such as belching, abdominal pain, bloating, and flatulence. Patients who achieve symptomatic relief should be advised to continue self-care measures as needed.

The health care provider should ask the patient to return or call after 1 week of self-treatment with dietary measures, nonprescription antiflatulents, or digestive enzymes so that outcomes can be assessed. Medical referral is necessary if any of the following is noted before or during treatment:

- Intestinal gas symptoms that are bothersome and or occur more often than occasionally (e.g., 3 times a month) and are associated with diarrhea or constipation
- Sudden change in the location of abdominal pain
- Significant increase in the severity or frequency of symptoms
- Sudden change in bowel function (suggestive of IBS)
- Emergence of accompanying signs and symptoms such as severe or persistent diarrhea or constipation; greasy or malodorous stools; GI bleeding (e.g., hematemesis, melena, hematochezia); fatigue; unintentional weight loss; or frequent nocturnal symptoms

Key Points for Intestinal Gas Complaints

- Limit self-treatment for intestinal gas to management of minor symptoms, and identify any exclusions for self-treatment ([Figure 14-1](#)).
- Counsel patients on dietary and other measures ([Table 14-3](#)) that may reduce the amount of intestinal gas. Certain foods ([Tables 14-1](#) and [14-2](#)) are more likely to cause gas formation and contribute to symptoms.
- Patients who experience symptoms with ingestion of lactose- or oligosaccharide-containing foods and who have no exclusions for self-treatment may use digestive enzymes (lactase replacement or α -galactosidase products).

- Probiotics or prebiotics may be helpful for patients with lactose intolerance who experience bloating or for patients with bloating associated with IBS.
- Antiflatulents such as activated charcoal and simethicone may be used, although the available evidence is contradictory regarding the ability of these agents to reduce the amount of intestinal gas formed.
- Referral to a primary care provider for further evaluation should be considered for patients with exclusions for self-treatment and for patients whose symptoms persist after initiation of simple treatment options (e.g., dietary modification, nonprescription medications).

Chapter 15: Constipation

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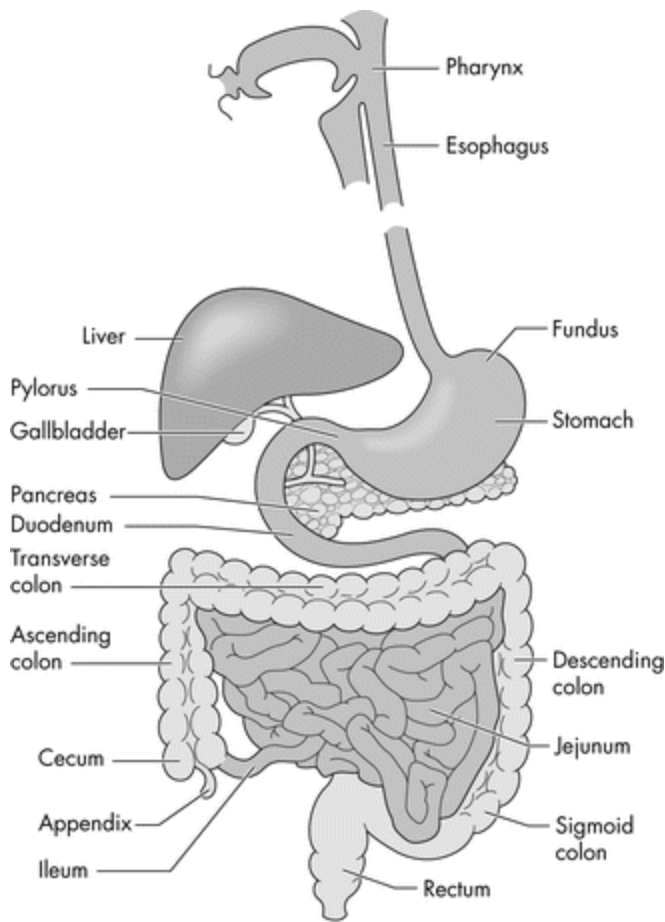
Editor's Note: This chapter is based on the 19th edition chapter of the same title, written by Kristin W. Weitzel and Jean-Venable "Kelly" R. Goode.

Constipation is a common gastrointestinal (GI) complaint. Although individual bowel habits differ, *constipation* in adults generally is defined as occurrence of fewer than 3 bowel movements per week, accompanied by straining and difficult passage of hard, dry stools.^{1,2} Patient descriptions of constipation may include (1) straining to have a bowel movement; (2) hard, dry stools; (3) small stools; (4) feeling as though bowel evacuation is incomplete; or (5) decreased stool frequency.^{2,3}

Constipation is common in male and female patients of all ages, with a wide range of reported prevalence rates in the general population of 2%–28%.^{1,4–6} Constipation is the reason for at least 2.5 million physician visits per year in the United States, with direct costs of diagnosis and treatment estimated at billions of dollars annually.⁷ It is reported more often in women, persons of non-White ancestry, children, and older people.^{1,4,8} Older adults (>65 years of age) are 5 times more likely to experience constipation than younger adults, and women are more than 3 times as likely as men to be affected.² Constipation also is a frequent complaint in late pregnancy and after childbirth.⁸ If untreated, constipation can lead to development of hemorrhoids or anal fissures, rectal prolapse, fecal impaction, or other complications.⁹

Pathophysiology of Constipation

Ingested food is retained in the stomach for about 3 hours and then in the small intestine for the same amount of time in persons with normal gastric motility (Figure 15–1). Tonic contractions of the stomach wall churn and knead ingested food, and peristaltic waves move along partially digested matter toward the duodenum.¹⁰



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Figure 15–1 Anatomy of the digestive system.

Contractions in the small intestine promote movement of nondigestible material into the large intestine. Fecal matter is stored in the sigmoid colon until defecation, which is controlled by both voluntary and involuntary reflexes.¹⁰ With normal gastric motility, fecal content within the colon triggers an involuntary peristaltic movement that propels fecal matter into the rectum, with relaxation of the internal anal sphincter. Voluntary tightening of the abdominal wall muscles with relaxation of the external anal sphincter then allows stool to pass. When defecating, the person may use the *Valsalva maneuver*, which entails a forceful increase in intra-abdominal pressure, actuated with an exhalation attempt against a closed glottis, to voluntarily initiate and promote passage of stool. Difficulty passing stool with constipation can lead to straining with significant force in an effort to promote defecation.¹⁰

Constipation may stem from primary or secondary mechanisms, with *primary*

constipation characterized as slower-than-normal GI transit time or a defecatory disorder (e.g., from pelvic floor dysfunction).^{2,6,8} *Secondary* causes include systemic, neurologic, and psychological disorders and/or structural abnormalities^{1-3,5,6} (**Table 15-1**). Inadequate dietary fiber and fluid intake may contribute to constipation. Dietary fiber dissolves or swells in the intestinal fluid, which increases fecal bulk to aid in stimulating peristalsis and eliminating stool. A diet low in calories, carbohydrates, or fiber may be associated with decreased fecal bulk and constipation. Inadequate intake of fluids may lead to development of dehydration, with consequent constipation.¹

Table 15-1 Selected Conditions Associated With Constipation

Structural
Colorectal or anorectal injury, inflammation, or damage (e.g., anal fissure)
Pelvic floor disorders
Structural abnormalities (e.g., tumors, hernias, strictures) leading to bowel obstruction
Systemic
Thyroid disorders
Diabetes mellitus
Irritable bowel syndrome
Neurologic disorders
Autonomic neuropathy
Multiple sclerosis
Parkinsonism
Postsurgical (anesthesia, immobility, fluid/electrolyte imbalance)
Cerebrovascular accident (stroke)
Dementia
Psychological
Depression

Eating disorders
Situational stress

Source: [References 1–3, 5, and 6](#).

Failing to respond to the urge to empty the bowel also can lead to constipation. When this urge is suppressed, rectal muscles can lose tonicity and become less effective, and nerve pathways stop sending the signal to defecate. Medication-associated constipation also can occur in the setting of multiple concomitant medical conditions or therapies^{2,3,11,12} ([Table 15–2](#)).

Table 15–2 Selected Drugs That May Induce Constipation

Analgesics (including nonsteroidal anti-inflammatory drugs)	Hematinics (especially iron)
Antacids (e.g., calcium and aluminum compounds, bismuth)	Hyperlipidemics (e.g., cholestyramine, pravastatin, simvastatin)
Anticholinergics (e.g., benztropine, glycopyrrolate)	Hypotensives (e.g., angiotensin-converting enzyme inhibitors, beta blockers)
Anticonvulsants (e.g., carbamazepine, divalproate)	Muscle relaxants (e.g., cyclobenzaprine, metaxalone)
Antidepressants (specifically, tricyclics such as amitriptyline, bupropion)	Opiates (e.g., morphine, codeine)
Antihistamines (e.g., diphenhydramine, loratadine)	Parkinsonism agents (e.g., bromocriptine)
Antimuscarinics (e.g., oxybutynin, tolterodine)	Polystyrene sodium sulfonate
Antineoplastics (e.g., vinca alkaloids)	Psychotherapeutic drugs (e.g., phenothiazines, butyrophenones)
Benzodiazepines (especially alprazolam and estazolam)	Sedative–hypnotics (e.g., zolpidem, benzodiazepines, phenobarbital)
Calcium channel blockers (e.g., verapamil, diltiazem)	Serotonin agonists (e.g., ondansetron)

Calcium supplements (e.g., calcium carbonate)	Sucralfate
Diuretics (e.g., hydrochlorothiazide, furosemide)	

Source: [References 2, 3, 11](#), and [12](#).

Clinical Presentation of Constipation

Constipation may manifest as self-reported decreased frequency or difficulty passing stools, anorexia, dull headache, lassitude, low back pain, abdominal discomfort, bloating, flatulence, and/or psychosocial distress.¹ Occasional bouts of temporary constipation usually can be managed with self-care measures. Constipation continuing over several weeks to months or that is complicated by concomitant conditions requires more sustained and aggressive therapy.^{13,14}

Long-standing or untreated constipation can lead to complications such as hemorrhoids, anal fissures, or rectal prolapse, fecal impaction, or rectal ulcers. Straining to defecate may be accompanied by blood pressure surges or precipitate cardiac rhythm disturbances secondary to altered hemodynamics.⁹

Algorithm: Constipation

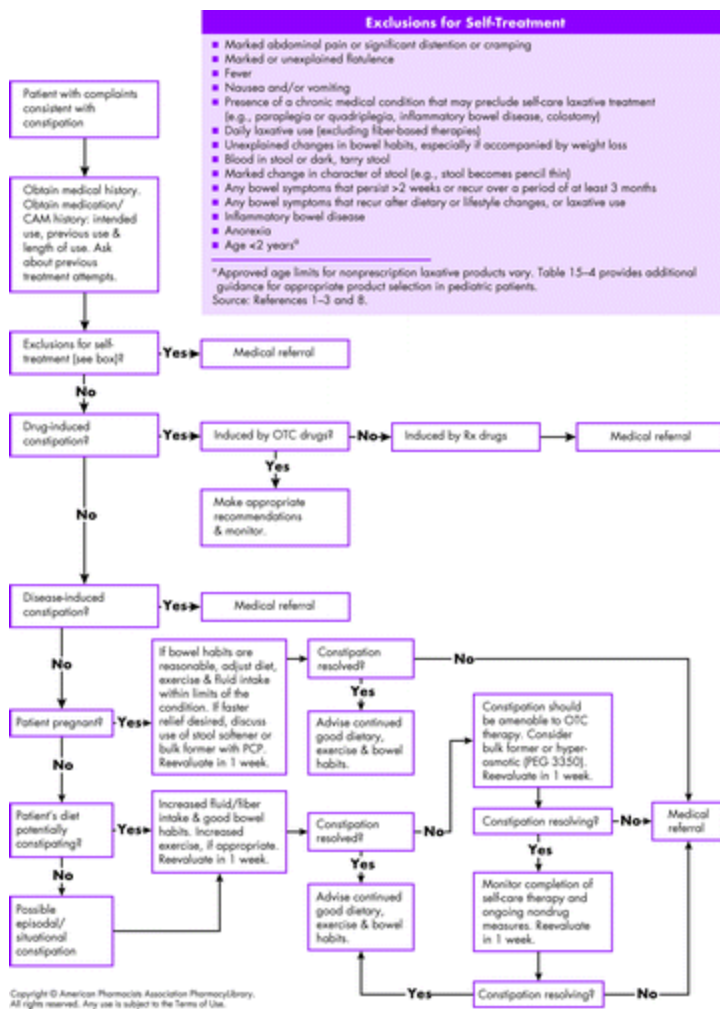


Figure 15-2 Self-care for constipation. Key: CAM = Complementary and alternative medicine; OTC = over-the-counter; PCP = primary care provider; PEG = polyethylene glycol; Rx = prescription.

Treatment of Constipation

Treatment Goals

The primary goals of treatment are (1) to relieve constipation and reestablish normal bowel function, (2) to establish dietary and exercise habits to help prevent recurrence, and (3) to promote the safe and effective use of laxative products if indicated.

General Treatment Approach

Initial management of constipation involves lifestyle changes, such as increasing intake of high-fiber food and fluids and regular exercise^{1-3,8} (Figure 15-2). Pharmacologic intervention can be used if more immediate relief is desired. Laxatives should be selected according to the age and health status of the patient, as well as the mechanism of action of the individual product. U.S. Food and Drug Administration (FDA) labeling for nonprescription products limits their use to short-term (<7 days) treatment without medical referral, which is consistent with the need for medical supervision of chronic constipation treatment.^{13,14} Accordingly, patients should not use any nonprescription laxative product for more than 7 days unless the therapy is directed by a health care provider. If rectal bleeding occurs at any time during the use of a laxative, or if constipation persists despite an appropriate laxative regimen, the patient should stop using the laxative and be referred for medical evaluation.^{1,15}

Nonpharmacologic Therapy

A balanced diet that incorporates fruits, vegetables, and whole grains helps to prevent constipation. The American Dietetic Association recommends an adult daily dietary fiber intake of 14 g per 1000 kcal, or 25 g for adult women and 38 g for adult men.^{16,17} (See Chapter 24 for information on dietary fiber types, sources, intake, and benefits.)

Added fiber increases stool mass and normalizes frequency of bowel movements. The longer stool is retained in the bowel, the more water is absorbed out of the bowel contents and into the intestinal cells, leading to hard stool consistency and difficulty in passing stool.¹⁷ Patients with the complaint of constipation should gradually increase their dietary intake of insoluble fiber (e.g., incorporating more whole grains, wheat bran, fruits, and vegetables into meals) and limit consumption of foods without fiber.^{8,17}

If dietary modifications are not effective, patients may use a commercially available fiber supplement. Many newer flavorless and texture-free fiber supplements (e.g., inulin) are classified as dietary supplements (Table 15-3).⁸ Other added-fiber supplements (e.g., psyllium, methylcellulose) are bulk-forming laxatives approved by FDA as nonprescription drugs (see “Pharmacologic Therapy”). A high-fiber diet or fiber supplement may take 3–5

days or longer for its effects to be realized. Significantly increasing dietary fiber initially may lead to erratic bowel movement frequency, flatulence, and abdominal discomfort. Gradually increasing fiber intake over a period of 1–2 weeks can improve tolerance.^{1,8,17} When adding dietary fiber, patients also should increase their fluid intake to approximately eight 8-ounce glasses per day. In pregnant and lactating women, an additional 300 mL and 750–1000 mL of fluid, respectively, are recommended.¹⁷

Table 15–3 Types of Fiber Supplements	
Type of Fiber	Example(s) of Common Brands
Products Classified as Bulk-Forming Laxatives ^a	
Methylcellulose	Citrucel
Calcium polycarbophil	FiberCon
Psyllium	Metamucil, Konsyl
Products Classified as Dietary Supplements	
Inulin	FiberChoice, Metamucil Clear & Natural
Partially hydrolyzed guar gum	Sunfiber
Powdered cellulose	Unifiber
Wheat dextrin	Benefiber

^a Products classified as bulk-forming laxatives are FDA labeled to treat constipation.

Source: Adapted with permission from [reference 8](#).

Behavior modifications (as “bowel training”) also can help promote bowel movements. Gastrocolic reflexes are strongest first thing in the morning and 30 minutes after a meal, so attempting a bowel movement at these times promotes defecation consistent with the body’s normal physiologic response. Low levels of physical activity have been shown to be associated with greater risk for constipation, so increasing beneficial activities in accordance with the

patient's capabilities can reduce this risk.^{1,18}

Pharmacologic Therapy

Recommendations for laxative products depend on the underlying cause of the constipation and individual patient factors and preferences. Constipation medications are classified by mechanism of action and include bulk-forming, hyperosmotic, emollient, lubricant, saline, and stimulant agents ([Table 15–4](#)).

Table 15–4 Dosage Guidelines for Nonprescription Laxative Products^a

Agent	Dosage Form/ Strength	Adults/ Children ≥12 Years	Children 6 to <12 Years ^b	Children 2 to <6 Years ^{b,c}
Bulk-Forming Agents				
Methylcellulose	Caplet: 500 mg	2 caplets up to 6 times daily	1 caplet up to 6 times daily	Not recommended for children <6 years, except under advice of a PCP
	Powder: 2 g/heaping tablespoon	Starting dose: 1 rounded tablespoon; increase as needed, 1 rounded tablespoon at a time, up to 3 times daily	Starting dose: 2.5 level teaspoons; increase as needed, 2.5 level teaspoons at a time, up to 3 times daily	Not recommended for children <6 years except under advice of a PCP
Calcium polycarbophil	Caplet: 625 mg	2 caplets 1–4 times daily	1 caplet 1–4 times daily	Not recommended for children <6 years, except under advice of a PCP
Psyllium (plantago seeds, ispaghula husks)	Capsule: psyllium husk, 0.52 g	5 capsules with 8 ounces of liquid (swallow 1 capsule at a time), up to 4	Not recommended for children <12 years except under advice of	Not recommended for children <6 years except under advice of

Agent	Dosage Form/ Strength	Adults/ Children ≥12 Years	Children 6 to <12 Years^b	Children 2 to <6 Years^{b,c}
		times daily	a PCP	a PCP
	<i>Powder: 3.4 g psyllium husk/scoop or “single- serving” packet of fiber product</i>	1 rounded tablespoon in 8 ounces of liquid, up to 3 times daily	½ of adult dose in 8 ounces of liquid, up to 3 times daily	Not recommended for children <6 years except under advice of a PCP
Hyperosmotic Agents				
Polyethylene glycol 3350	<i>Powder: 17 g/ capful</i>	17 g in 4–8 ounces of beverage once daily in adults and children ≥17 years	Not recommended for children <17 years, except under advice of a PCP	Not recommended for children <17 years, except under advice of a PCP
Glycerin	<i>Rectal solid suppository: 2 g</i>	1 suppository, or as directed by a PCP	1 suppository, or as directed by a PCP	Not recommended for children <6 years except under advice of a PCP
	<i>Rectal solid suppository: 1 g (pediatric formulation)</i>	–	–	1 suppository, or as directed by a PCP
	<i>Rectal liquid suppository: 5.6 g glycerin/5.5 mL</i>	1 suppository, or as directed by a PCP	1 suppository, or as directed by a PCP	Not recommended for children <6 years, except under advice of a PCP
	<i>Rectal liquid suppository: 2.8 g glycerin/2.7 mL (pediatric formulation)</i>	–	–	1 suppository, or as directed by a PCP

Agent	Dosage Form/ Strength	Adults/ Children ≥12 Years	Children 6 to <12 Years^b	Children 2 to <6 Years^{b,c}
Emollient Agents				
Docusate sodium	<i>Capsules:</i> 50 mg and 100 mg	50–300 mg daily in single or divided doses	50–150 mg daily in single or divided doses	50–150 mg daily in single or divided doses
	<i>Syrup:</i> 60 mg/15 mL	1–6 tablespoons (15–80 mL) daily, or as directed by a PCP, in single or divided doses (doses must be given in 6–8 ounces of milk or juice to prevent throat irritation)	1–2 ½ (15–37.5 mL) tablespoons daily, or as directed by a PCP, in single or divided doses (doses must be given in 6–8 ounces of milk or juice to prevent throat irritation)	1–2 ½ tablespoons (15–37.5 mL) daily, or as directed by a PCP, in single or divided doses (doses must be given in 6–8 ounces of milk or juice to prevent throat irritation)
	<i>Syrup:</i> 50 mg/15 mL (pediatric formulation)	—	1–3 tablespoons (15–45 mL) daily, in single or divided doses (doses must be given in 6–8 ounces of milk or juice to prevent throat irritation)	1–3 tablespoons (15–45 mL) daily, in single or divided doses (doses must be given in 6–8 ounces of milk or juice to prevent throat irritation)
Docusate calcium	<i>Capsule:</i> 240 mg	1 capsule daily for several days, or until bowel movements are normal	Not recommended for children <12 years, except under advice of a PCP	Not recommended for children <6 years, except under advice of a PCP
Lubricant Agent				
Mineral oil ^d	<i>Liquid</i> (oral formulation)	1–3 tablespoons (15–45 mL); maximum 3 tablespoons (45	1–3 teaspoons (5–15 mL); maximum 3 teaspoons (15	Not recommended for children <6 years except

Agent	Dosage Form/ Strength	Adults/ Children ≥12 Years	Children 6 to <12 Years^b	Children 2 to <6 Years^{b,c}
		mL) in 24 hours	mL) in 24 hours	under advice of a PCP
		6–15 teaspoons (30–75 mL) daily, or as directed by a PCP	2–5 teaspoons (10–25 mL) daily, or as directed by a PCP	Not recommended for children <6 years except under advice of a PCP
		1 bottle as directed	½ bottle as directed	½ bottle as directed
Saline Laxative Agents				
Magnesium citrate	<i>Liquid:</i> 10 fluid ounces (300 mL)	½–1 bottle (150–300 mL) as directed	⅓–½ bottle (100–150 mL) as directed	Not recommended for children <6 years except under advice of a PCP
Magnesium hydroxide	<i>Liquid:</i> 400 mg/5 mL	2–4 tablespoons (30–60 mL) daily as single or divided doses	1–2 tablespoons (15–30 mL) daily as single or divided doses	Not recommended for children <6 years except under advice of a PCP
	<i>Concentrated liquid:</i> 2400 mg/15 mL	1–2 tablespoons (15–30 mL) daily as single or divided doses	½–1 tablespoon (7.5–15 mL) daily as single or divided doses	Not recommended for children <6 years except under advice of a PCP
	<i>Chewable tablet:</i> 311 mg per tablet	8 tablets once in a 24-hour period, preferably at bedtime, in divided doses or as directed by a PCP	4 tablets once in a 24-hour period, preferably at bedtime, in divided doses or as directed by a PCP	Children 3–5 years: chew 2 tablets once in a 24-hour period, preferably at bedtime, in divided doses or as directed by a

Agent	Dosage Form/ Strength	Adults/ Children ≥12 Years	Children 6 to <12 Years^b	Children 2 to <6 Years^{b,c}
				PCP
				Not recommended for children <3 years except under advice of a PCP
	<i>Chewable tablet</i> : 400 mg/tablet (pediatric formulation)	—	3–6 tablets daily in single or divided doses	1–3 tablets daily in single or divided doses
Monobasic sodium phosphate/ dibasic sodium phosphate	<i>Rectal liquid enema</i> : 118 mL	1 bottle, as directed	Not recommended for children <12 years, except under advice of a PCP	Not recommended for children <6 years, except under advice of a PCP
	<i>Rectal liquid enema</i> : 197 mL	1 bottle, as directed	Not recommended for children <12 years, except under advice of a PCP	Not recommended for children <6 years, except under advice of a PCP
	<i>Rectal liquid enema</i> : 59 mL (pediatric formulation)	—	Children 5–11 years: 1 bottle or as directed by a PCP	Children 2–5 years: ½ bottle
Magnesium sulfate (Epsom salt) ^d	<i>Solid</i> : magnesium sulfate USP	2–6 level teaspoons (10–30 g) daily ^d	1–2 level teaspoons (5–10 g) daily ^d	Not recommended for children <6 years except under advice of a PCP
Stimulant Agents				
Senna	<i>Tablets</i> : 8.6	Starting dose: 2	Starting dose: 1	Starting dose: ½

Agent	Dosage Form/ Strength	Adults/ Children ≥12 Years	Children 6 to <12 Years ^b	Children 2 to <6 Years ^{b,c}	
	mg sennosides	tablets once daily	tablet once daily	tablet once daily	
		Maximum dose: 4 tablets twice daily	Maximum dose: 2 tablets twice daily	Maximum dose: 1 tablet twice daily	
	<i>Tablets or chocolate pieces: 15 mg sennosides</i>	2 tablets or 2 chocolate pieces 1-2 times daily	1 tablet or 1 chocolate piece 1-2 times daily	Not recommended for children <6 years, except under advice of a PCP	
	<i>Tablets: 17.2 mg sennosides</i>	Starting dose: 1 tablet once daily	Starting dose: ½ tablet once daily	Not recommended for children <6 years, except under advice of a PCP	
		Maximum dose: 2 tablets twice daily	Maximum dose: 1 tablet twice daily		
	<i>Pills: 25 mg sennosides</i>	2 pills 1-2 times daily	1 pill 1-2 times daily	Not recommended for children <6 years, except under advice of a PCP	
	<i>Liquid^e: senna concentrate 33.3 mg senna pod concentrate/ mL (pediatric formulation [e.g., Fletcher's Laxative for Kids])</i>	—	Age 6-15 years: 2-3 teaspoons (10-15 mL) 1-2 times daily	1-2 teaspoons (5-10 mL) 1-2 times daily	
	<i>Liquid^e: sennosides</i>	2-3 teaspoons (10-15 mL) once	1-1½ teaspoons (5-7.5 mL) once a	½-¾ teaspoon (2.5-3.75 mL)	

Agent	Dosage Form/ Strength	Adults/ Children ≥12 Years	Children 6 to <12 Years^b	Children 2 to <6 Years^{b,c}	
	1.8 mg sennosides/ mL	a day	day	once a day	
Bisacodyl	<i>Tablets</i> : 5 mg	1–3 tablets (usually 2) once daily	1 tablet daily	Not recommended for children <6 years except under advice of a PCP	
	<i>Rectal solid suppository</i> : 10 mg	1 suppository in a single daily dose	½ suppository in a single daily dose	Not recommended for children <6 years except under advice of a PCP	
Castor oil ^d	<i>Liquid</i>	1–4 tablespoons (15–60 mL) in a single daily dose; maximum of 4 tablespoons daily ^d	1–3 teaspoons (5–15 mL) in a single daily dose; maximum of 3 teaspoons daily ^d	Not recommended for children <6 years except under advice of a PCP	

^a All doses are based on FDA-labeled instructions and are for oral products, unless indicated otherwise.

^b All doses for children are listed as those for ages 2 to <6 years or 6 to <12 years, unless otherwise indicated in FDA-labeled dosing instructions. In these cases, FDA-labeled age ranges are provided within the table.

^c No recommended dosages exist for children <2 years of age, except under the advice and supervision of a PCP.

^d Although magnesium sulfate (Epsom salt) and castor oil are approved as nonprescription laxatives, they are not recommended, because safer, better-tolerated, and well-studied alternatives are available. Self-care use of mineral oil also is discouraged in most cases. See text under “Pharmacologic Therapy” for specific recommendations on appropriate use of each agent.

^e Liquid senna products vary in concentration and dosing. Take care to ensure that patients are following FDA-labeled dosing instructions with use of these products, especially in pediatric patients.

Key: FDA = U.S. Food and Drug Administration; OTC = over-the-counter; PCP = primary care provider.

Bulk-Forming Agents

Bulk-forming laxatives include methylcellulose, polycarbophil, and psyllium-containing products. These agents are most often recommended for treatment of constipation, because their effects most closely approximate the body's physiologic process.^{1,5,8} Available dosage forms include tablets or capsules, powders to be mixed with water or other liquids, and fiber chews, wafers, or “gummies.”

The usual time to onset of action for bulk-forming laxatives is 12–24 hours, but effects may take up to 72 hours. These agents are indicated for short-term therapy and may be useful in (1) patients on low-fiber diets, (2) new mothers in the postpartum period, (3) older adults, and (4) patients with colostomies, irritable bowel syndrome, or diverticular disease. This type of laxative also is used prophylactically in patients who should avoid straining during a bowel movement (e.g., with recent surgery). Dosages vary according to the type of product ([Table 15–4](#)). Exceeding the recommended dose may lead to increased flatulence or obstruction if appropriate fluid intake is not maintained.

Bulk-forming agents have few systemic adverse effects, with abdominal cramping and flatulence most commonly reported. If not taken with adequate fluid, bulk-forming laxatives may swell in the throat or esophagus, potentially causing choking. These products should be avoided by patients with swallowing difficulties or esophageal strictures or those on fluid-restricted diets.¹⁹ Because of the danger of fecal impaction or intestinal obstruction, patients with intestinal ulcerations, stenosis, or disabling adhesions should not take bulk-forming products. The onset of chest pain, vomiting, difficulty swallowing, or difficulty breathing after use warrants immediate medical attention.²⁰ Acute bronchospasm has been associated with accidental inhalation of dry hydrophilic mucilloid, as well as hypersensitivity reactions to psyllium characterized by anaphylaxis.²¹ Persons with a recognized sensitivity

to inhaled or ingested psyllium should avoid these products.

Calcium polycarbophil can contain up to 150 mg (7.6 mEq) calcium per tablet, which may be clinically relevant in patients at risk for hypercalcemia (e.g., renal disease). The sugar content of bulk-forming agents should be considered in patients with diabetes or restricted caloric intake. Although bulk-forming laxatives are not systemically absorbed, they can interfere with the absorption of oral medications as a consequence of physical binding in the GI tract or other mechanisms ([Table 15–5](#)).

Table 15–5 Clinically Important Drug–Drug Interactions With Nonprescription Laxative Agents

Laxative Agent	Interacting Drug(s)	Potential Mechanism of Interaction	Management/ Preventive Measures
Bulk-forming laxatives (e.g., psyllium)	Digoxin, anticoagulants, salicylates, and potentially other oral drugs	Interference with drug absorption	Separate dosing of prescription oral medications by at least 2 hours
Docusate salts	Mineral oil	Increased absorption of mineral oil	Avoid concurrent use
Magnesium citrate	Fluoroquinolone and tetracycline antibiotics	Decreased drug absorption	Avoid oral magnesium citrate within 1–3 hours of ingestion of oral tetracyclines or fluoroquinolones
Magnesium hydroxide	Captopril, cefdinir, some oral bisphosphonates, gabapentin, iron salts, nitrofurantoin, phenothiazines, phenytoin, rosuvastatin	Decreased oral bioavailability and/or rate or extent of drug absorption	Separate dosing by at least 2 hours for most agents
Magnesium hydroxide	Ketoconazole, itraconazole, fluoroquinolone, and tetracycline antibiotics, levothyroxine	Decreased drug absorption	Avoid magnesium hydroxide for at least 4 hours before or up to 3 hours after ingestion of interacting agent
Bisacodyl	Milk products or drugs that raise gastric pH (e.g., proton	Premature dissolution of the bisacodyl	Avoid milk products or interacting drugs within

Laxative Agent	Interacting Drug(s)	Potential Mechanism of Interaction	Management/ Preventive Measures
	pump inhibitors)	enteric coating, leading to gastric irritation or dyspepsia	1 hour before or after ingestion of bisacodyl

Hyperosmotic Agents

Hyperosmotic agents include polyethylene glycol 3350 (PEG 3350) and glycerin ([Table 15–4](#)). These products contain large, poorly absorbed ions or molecules that draw water into the colon or rectum through osmosis to stimulate a bowel movement.²²

PEG 3350 is available for self-care use in patients 17 years of age or older. It is supplied as a powder for oral administration and usually is taken as 17 g of powder (approximately 1 capful or 1 packet) mixed into 4–8 ounces of water, once daily as needed. PEG 3350 has minimal systemic absorption, with less than 1% of each dose absorbed and excreted in the urine. PEG 3350 usually produces a bowel movement in 12–72 hours, but onset of effect may take up to 96 hours.

PEG 3350 is safe and effective for the short-term treatment of occasional constipation, with few adverse effects.²³ The most common adverse effects are bloating, abdominal discomfort, cramping, and flatulence. FDA-approved labeling indicates that patients who have renal disease or irritable bowel syndrome should be cautioned to consult their primary care provider before using PEG 3350. No clinically significant drug–drug interactions have been reported with PEG 3350.

Glycerin is available as a suppository for lower bowel evacuation ([Table 15–4](#)). Glycerin suppositories usually produce a bowel movement within 15–30 minutes and are safe for occasional use in all approved age groups. Adverse effects are limited, although rectal irritation is possible with overdose. Glycerin suppositories should be avoided in patients with preexisting rectal irritation.

Emollients

Emollients, also called stool softeners, are anionic surfactants that act in the small and large intestine to increase the wetting efficiency of intestinal fluid, facilitating a mixture of aqueous and fatty substances to soften the fecal mass (Table 15–4). They can be used to prevent straining and painful defecation in patients with anorectal disorders or in those who should avoid straining (e.g., with recent abdominal or rectal surgery). Although stool softeners can be taken for occasional constipation, these agents are used more often in combination with a stimulant laxative (e.g., senna, bisacodyl) for opioid-induced constipation.^{19,24} (See the box “A Word About Opioid-Induced Constipation.”)

Docusate, available as a sodium and a calcium salt, usually works within 12–72 hours, up to 3–5 days may be required for complete effects to be obtained.⁸ Although no clinical differences between the salt forms are recognized, availability of docusate sodium in multiple strengths and dosage forms leads to its more frequent use. Docusate sodium is supplied as a capsule or syrup in multiple strengths; docusate calcium is available as a 240 mg capsule. Docusate is not appreciably absorbed from the GI tract and does not hamper absorption of nutrients from the intestinal tract. It generally is well tolerated and is associated with minimal drug interactions (Table 15–5). Larger-than-recommended doses may result in weakness, sweating, muscle cramps, and irregular heartbeat.

Lubricants

Mineral oil (liquid petrolatum) is the only nonprescription lubricant product. Mineral oil softens fecal contents by coating stool and preventing colonic absorption of fecal water. It is available in liquid form for oral or rectal administration (Table 15–4). Time to onset of action for mineral oil is approximately 6–8 hours after oral administration and 5–15 minutes after rectal administration.

The most significant acute safety concern with mineral oil is lipid pneumonia resulting from aspiration into the lungs after an oral dose. Mineral oil should not be taken before lying down and should be avoided in patients at risk for aspiration. FDA labeling for mineral oil products includes a warning against its use in patients younger than 6 years, pregnant women, immobile or older

adults, and persons with difficulty swallowing.

Taking larger-than-recommended doses of mineral oil can cause oil leakage through the anal sphincter, anal pruritus (pruritus ani), cryptitis, or other perianal conditions. With repeated and prolonged use of mineral oil, the droplets may be deposited in the mesenteric lymph nodes and potentially the intestinal mucosa, liver, and spleen as well, where they may elicit a typical foreign body reaction. Mineral oil may impair the absorption of fat-soluble vitamins A, D, E, and K. Because of these and other safety concerns, potential drug interaction with docusate ([Table 15–5](#)), and the availability of better treatment alternatives, use of mineral oil to treat constipation should be avoided if possible.⁸

Saline Laxatives

Saline laxatives include magnesium citrate, magnesium hydroxide, dibasic sodium phosphate, monobasic sodium phosphate, and magnesium sulfate. They are available in liquid or solid form for oral administration and in liquid form for rectal administration ([Table 15–4](#)). Saline laxatives draw water into the small and large intestine (oral products) or colon (rectal forms) by osmosis, thereby increasing intraluminal pressure and promoting GI motility. Saline laxatives are used to treat constipation or for acute bowel evacuation required before a procedure (e.g., colonoscopy).

Oral magnesium hydroxide is appropriate for occasional constipation in otherwise healthy patients. At standard doses, magnesium hydroxide produces a bowel movement within 30 minutes to 6 hours of administration.⁸ Other saline laxatives such as magnesium citrate are more commonly used for acute catharsis (e.g., as preparation for a colonoscopy). With use of saline agents for these purposes, the time to onset of action is 30 minutes to 3 hours for oral doses and 2–15 minutes for rectal doses. Although magnesium sulfate (Epsom salt) is labeled for nonprescription use, it should be avoided, because safer laxatives are available.

Adverse effects of saline laxatives may include abdominal cramping, nausea, vomiting, or dehydration. Patients who cannot tolerate fluid loss of significant degree should not use saline laxatives. In patients who are not on fluid restriction, oral doses of magnesium salts should be followed by at least 8 ounces of water to prevent dehydration. If used long-term or at higher-than-

recommended doses, saline laxatives containing magnesium can cause electrolyte imbalances, including hypermagnesemia.⁸ Magnesium-containing laxatives should be avoided in patients on sodium-, phosphate-, or magnesium-restricted diets and in persons at increased risk for magnesium toxicity (e.g., newborns, older adults, patients with renal impairment). In making recommendations for such products, health care providers should consider potential drug–drug interactions with magnesium-containing laxatives ([Table 15–5](#)).

Products containing sodium phosphate can cause hyperphosphatemia, hypocalcemia, and hypernatremia. Caution is warranted with use of such products in persons with renal impairment, those on sodium-restricted diets, and/or patients taking medications that may affect serum electrolyte levels (e.g., diuretics).⁸ Sodium phosphate products are contraindicated in patients with congestive heart failure. Additionally, rectally administered sodium phosphate should be avoided in patients with megacolon, GI obstruction, imperforate anus, or colostomy.²⁵

Acute phosphate nephropathy and renal impairment have been reported with use of sodium phosphate products for bowel cleansing, and the use of nonprescription oral sodium phosphate solutions is restricted to treatment of constipation only (i.e., not in bowel preparations). In 2014, an FDA drug safety communication recommended that patients not exceed one dose of such agents in a 24-hour period and advised caution with use in high-risk populations (e.g., age older than 55 years, baseline kidney disease).²⁵

Stimulant Agents

Stimulant laxatives are classified according to their chemical structure and pharmacologic activity as anthraquinones (e.g., senna) or diphenylmethanes (e.g., bisacodyl). FDA has deemed formerly available products containing cascara sagrada, casanthranol, and phenolphthalein as “not safe and effective.”^{26,27} Because some of these unapproved agents are marketed as dietary supplements, they may be available in some pharmacies but should not be recommended as therapeutics. Although rhubarb and aloe were not included in FDA rulings, neither of these should be recommended by the health care provider.

Stimulant laxatives ([Table 15–4](#)) work primarily in the colon to increase

intestinal motility by local mucosal irritation by acting on the intramural nerve plexus of intestinal smooth muscle. They also increase secretion of water and electrolytes in the intestine.⁵ The time to onset of action for senna and bisacodyl is usually 6–10 hours after oral administration, but onset of effect may take up to 24 hours. Bisacodyl suppositories usually take effect 15–60 minutes after administration.

Bisacodyl, administered orally or rectally, also is a component of bowel preparation regimens before colonoscopy or other procedures. Stimulant laxatives also may be used with docusate to prevent or treat constipation in patients taking chronic opioids.^{19,24} (See the box “A Word About Opioid-Induced Constipation.”) Overdoses of stimulants may lead to sudden vomiting, nausea, diarrhea, or severe abdominal cramping and require prompt medical attention.

Major hazards of stimulant laxative use include severe cramping, electrolyte and fluid deficiencies, enteric loss of protein, malabsorption caused by excessive hypermotility and catharsis, and hypokalemia. At very high doses, all stimulants may produce cramping, colic, increased mucus secretion, and in some patients, excessive evacuation of fluid. Stimulants can be effective but may be overused.^{28–31} (See the box “A Word About Laxative Overuse.”)

Prolonged use of senna also can cause a harmless, reversible melanotic pigmentation of the colonic mucosa (melanosis coli), which may be seen at sigmoidoscopy or colonoscopy or in rectal biopsy specimens. Senna may color urine pink to red, red to violet, or red to brown, and its presence may affect interpretation of the phenolsulfonphthalein test.

Enteric-coated bisacodyl tablets prevent irritation of the gastric mucosa. Such products should not be broken, crushed, chewed, or given with agents that increase gastric pH. The administration of bisacodyl tablets within 1 hour of ingestion of antacids, histamine type 2 (H₂) receptor antagonists, proton pump inhibitors, or milk results in rapid erosion of the tablet’s enteric coating, which may lead to gastric or duodenal irritation.

Although castor oil historically has been viewed as a stimulant laxative, its exact mechanism is unknown.³¹ Castor oil acts quickly and has significant laxative effects. Prolonged use of castor oil may result in excessive loss of fluid, electrolytes, and nutrients. Its use in the self-care setting is discouraged, because safer and better-tolerated alternatives are available.^{8,19}

Combination Products

Combination laxative products also are available ([Table 15–6](#)). For example, some products contain a stimulant and an emollient (e.g., senna with docusate sodium) or a stimulant and psyllium. Other available combination oral products include those with psyllium, bisacodyl, docusate, or another agent as the principal ingredient and glycerin as an adjunctive agent.

Table 15–6 Selected Nonprescription Laxative Products	
Trade Name	Primary Ingredient(s)
Bulk-Forming Laxatives	
Citrucel Powder	Methylcellulose 2 g/heaping tablespoon
Citrucel Sugar Free Powder	Methylcellulose 2 g/heaping tablespoon
FiberCon Caplets	Calcium polycarbophil 625 mg/caplet
Metamucil Smooth Texture, Sugar Free Orange Flavor Powder/Individual Packets	Psyllium fiber 3 g/packet
Emollient Laxatives	
Colace Capsules	Docusate sodium 100 mg/capsule
Lubricant Laxatives	
Fleet Mineral Oil Enema	Mineral oil 100%
Kondremul Emulsion	Mineral oil 55%
Saline Laxatives	
Magnesium Citrate Oral Solution	Magnesium citrate 1.745 g/30 mL
Fleet Enema	Monobasic sodium phosphate 19 g/118 mL; dibasic sodium phosphate 7 g/118 mL
Pedia-Lax Enema	Monobasic sodium phosphate 9.5 g/59 mL; dibasic sodium phosphate 3.5 g/59 mL
Phillips' Milk of Magnesia Suspension	Magnesium hydroxide 400 mg/5 mL
Hyperosmotic Laxatives	

Trade Name	Primary Ingredient(s)
Fleet Glycerin Suppository (adult size)	Glycerin 2 g/suppository
MiraLAX	Polyethylene glycol 3350 17 g/capful
Stimulant Laxatives	
Dulcolax Tablets	Bisacodyl 5 mg/tablet
Senokot Tablets	Sennosides 8.6 mg/tablet
Fletcher's Laxative for Kids	Senna concentrate 33.3 mg/mL
Combination Laxatives	
Senokot-S Tablets	Sennosides 8.6 mg/tablet; docusate sodium 50 mg/tablet

Patients should be counseled that combining laxatives is associated with a greater likelihood of adverse effects, because most such products contain a stimulant. If a stimulant and a stool softener are combined, the potential for adverse effects depends largely on the stimulant. However, if a stimulant and a saline product are combined, the potential for such effects is enhanced, because both agents have significant effects on the intestine.

Pharmacotherapeutic Comparison

Head-to-head comparison studies of solely nonprescription laxatives are largely lacking, because most nonprescription laxative ingredients became available before the current emphasis on comparative evidence. With many products, much of what is practiced has been learned through observation and a common-sense approach. For example, a bulk-forming product should soften the stool by its normal action. Because both a stool softener and a bulk-forming agent take approximately the same length of time to work, a bulk-forming agent may be the correct choice for some patients who require stool softening. Although stimulants and saline-type laxatives have been used widely for self-care, the health care provider should recommend a product with the lowest likelihood of untoward effects. Of the available nonprescription agents, PEG 3350 is considered by many professional groups and practitioners

to have the strongest evidence for efficacy and safety.³²

Product Selection Guidelines

In decisions regarding the use of any laxative to treat uncomplicated constipation, an important consideration is that normal defecation empties only the rectum and the descending and sigmoid segments of the colon. A bulk-forming laxative exerts its effects in a manner that most closely duplicates this normal physiologic process, and the use of bulking agents often is recommended as the initial treatment choice for self-care for acute constipation. However, bulk-forming laxatives may take up to 72 hours or longer for onset of effect. If faster onset is desired, or if a bulk-forming agent is ineffective or inappropriate, the hyperosmotic PEG 3350 also is considered a first-line agent, in view of its effectiveness and favorable adverse effect profile. If PEG 3350 is unable to produce a satisfactory response, addition of a stimulant (e.g., bisacodyl) should be considered.^{6,8,9} In each case, the lowest effective dose should be used, and the dose should be reduced once symptoms subside. Patients who fail to achieve a therapeutic response after 7 days of self-treatment require medical referral.

Special Populations

CHILDREN. Constipation in children generally is defined as a delay or difficulty in achieving bowel movements over a period of 2 weeks or longer; [Table 15–4](#) provides age-based definitions and laxative dosing recommendations for children.^{33,34} Constipation affects 16%–37% of children and is the most common cause of abdominal pain in this age group.^{15,35} Factors that can alter bowel habits in children include unavailability of toilet facilities, emotional distress, febrile illness, chronic medical conditions (e.g., cystic fibrosis, hypothyroidism), family conflict, dietary changes (e.g., switching from human to cow milk), fear of defecation (or the associated environment), or a change in daily routine or environment.³³ Children who experience pain on straining to pass stools may further avoid bowel movements or withhold stool, resulting in worsening symptoms and a fear of toileting.^{15,33}

Evaluation of constipation in children should begin with determination of exclusions for nonprescription therapy ([Figure 15–2](#)). Constipation in children may manifest as fecal impaction, and children with suspected impaction (as indicated by abdominal cramping; rectal bleeding; small, semifformed stools;

fecal soiling; and/or constipation accompanied by watery diarrhea) should be referred for further evaluation.^{15,33}

Mild constipation in children often can be relieved with dietary or behavioral modifications, such as increasing intake of fluid and fruit juices containing sorbitol (e.g., prune, apple).^{15,33} Once solid foods are introduced, incorporation of high-fiber cereals or grains, vegetables, and fruits into the diet also may relieve symptoms. The recommended dietary fiber intake (in grams) for children older than 2 years should equal or exceed their age plus 5 g/day.¹⁷ Parents or caregivers should establish a regular stooling time for toilet-trained children (usually after a morning meal) and develop a supportive system (e.g., charts, stickers) for positively reinforcing bowel movements. Children should be encouraged to promptly heed the urge to pass a bowel movement, to avoid negative consequences of retaining stool in the rectum (e.g., increased hardening, pain, abdominal distention).^{33,34} In older children, laxatives often can be avoided altogether with adherence to suggested dietary and fiber guidelines.

If dietary or behavior modifications are insufficient, pharmacologic therapy is indicated ([Table 15–4](#)). Nonprescription laxatives approved for self-care in children 2 to <6 years of age include oral docusate sodium, magnesium hydroxide, and senna. Rectal use of glycerin, mineral oil, or sodium phosphate products also is approved in this age group. Oral products approved for children 6 up to 12 years of age include methylcellulose, calcium polycarbophil, docusate sodium, mineral oil, magnesium citrate, magnesium hydroxide, magnesium sulfate, senna, bisacodyl, and castor oil. (See “Pharmacologic Therapy” for recommendations on use of individual agents. See also [Chapter 11](#), under “Special Populations,” for FDA requirements for dispensing devices included in liquid nonprescription products.) Oral use of PEG 3350 is not FDA-approved for patients younger than 17 years, but its off-label use in children is increasing. Rectal products approved for children 6 up to 12 years of age include glycerin suppositories, mineral oil, sodium phosphate, and bisacodyl.

If medication is needed for the occasional relief of temporary constipation in children 2 to <6 years of age, oral docusate sodium or magnesium hydroxide can be recommended first.^{15,33} Docusate sodium may be especially helpful if the primary complaint is difficulty passing dry, hard stools. If faster relief is needed, the health care provider can recommend pediatric-size glycerin suppositories. Oral senna or magnesium citrate and rectal mineral oil or

sodium phosphate enemas should be reserved for use when other treatments fail or at the direction of a health care provider.^{15,33–36}

In children 6 up to 12 years of age, bulk-forming agents, docusate sodium, or magnesium hydroxide can be recommended for the occasional relief of temporary constipation, with oral stimulants reserved for when other treatments fail.^{15,33–36} For faster relief, glycerin or bisacodyl suppositories can be recommended, with mineral oil or sodium phosphate enemas reserved for when other treatments fail, or at the direction of a health care provider.¹⁵ Use of magnesium sulfate (Epsom salt) and castor oil should be avoided owing to the availability of safer, better-tolerated, and well-studied laxatives.^{33,34}

PATIENTS OF ADVANCED AGE. Prevalence of constipation among persons 65 years of age and older is higher than in the general population, with 15%–20% of community-dwelling older adults and up to 50% of nursing home residents reporting constipation.⁵ Older people are at greater risk for constipation because of aging-related dietary changes (e.g., reduced caloric, fiber, and/or fluid intake); decreased physical activity; presence of comorbid conditions (e.g., parkinsonism, depression); increased use of medications that cause constipation (e.g., opioids, anticholinergics); and physiologic changes with age (e.g., absorption, distribution, metabolism, excretion).^{5,18}

Pharmacists should conduct a medication review to identify comorbid conditions and drug therapies (see also [Chapter 2](#)). Lifestyle modifications should be recommended first, including slowly increasing fiber and fluid, adding prunes or prune juice to the diet, physical activity as tolerated, and bowel training.^{5,19} An important clinical consideration is recognition of fluid or other restrictions associated with comorbid conditions (e.g., congestive heart failure, renal failure) in older adults.⁵

If medication adjustments and/or lifestyle changes are insufficient, the health care provider should recommend pharmacologic therapy, starting with bulk-forming laxatives. Patients who are dehydrated, very frail, immobile, or unable to drink adequate fluid to prevent mechanical obstruction or fecal impaction should not use bulk-forming laxatives. If these laxatives cannot be used or do not provide sufficient relief, or if faster onset of effect is desired, PEG 3350 also is used as a first-line option because of its efficacy and tolerability.^{5,37} Stool softeners (e.g., docusate) may be helpful along with other first-line options in older adults with anal fissures or hemorrhoids associated with painful defecation.¹⁸

Some nonprescription laxatives should be avoided or used only with caution in older adults, including mineral oil (increased risk of aspiration) and saline laxatives (risk of fluid or electrolyte depletion, magnesium toxicity, or drug interactions).⁵ Older adults are sensitive to fluid and electrolyte shifts, particularly those on diuretics or with fluid restrictions.^{5,18}

Older adults may require rectally delivered therapy with a suppository or enema, especially if fecal impaction is suspected. Rectal preparations generally are considered to be safe in this age group, although comparative safety and effectiveness evidence is limited.^{5,38} Older adults may be more susceptible to adverse effects from sodium phosphate products, and these agents should be avoided or used with caution in this population (see the box “A Word About Laxative Overuse”).³⁸

PREGNANCY AND LACTATION. Constipation affects up to one third of women throughout pregnancy and the postpartum period.³⁹ Contributing factors include compression of the colon by the growing uterus, increasing progesterone levels, low fluid and fiber intake, and the constipating effects of iron and calcium in prenatal supplements.³⁹

Dietary measures (e.g., increasing fiber and fluids) are first-line interventions. The addition of a laxative is indicated only after a nondrug approach is determined to be insufficient.³⁹ (Refer to the Preface for a detailed explanation of the pregnancy data.) Bulk-forming laxatives should be recommended first.^{39–41} Docusate also may be used for patients who have primarily dry, hard stools.⁴¹ If needed, short-term use of senna or bisacodyl is considered a low-risk approach in pregnancy.^{40,41} Some experts also consider PEG 3350 to be a first-line choice in pregnancy because very little is absorbed systemically.⁴¹ Short-term use of senna or bisacodyl is preferred by some practitioners, however, because more data are available for use of these agents in pregnancy.^{39,40} In more severe cases, or when the safety of a laxative product is questionable, consultation with the patient’s regular health care provider is recommended before laxative use.

Of note, with certain laxatives, including castor oil, mineral oil, and saline laxatives, specific risks have been recognized with use in pregnancy, so such products should be used only very cautiously or perhaps avoided altogether in this setting. Castor oil has been associated with uterine contraction and rupture, and mineral oil may impair maternal fat-soluble vitamin absorption. High doses or long-term use of saline laxatives (e.g., magnesium hydroxide)

may cause electrolyte imbalances and generally should be avoided.^{40,41}

Laxatives also may be used post partum to reestablish normal bowel function. Senna, bisacodyl, PEG 3350, and docusate are considered to be compatible with breastfeeding or to carry a low risk of adverse effects in this setting.^{40,42,43} These agents are minimally absorbed or do not accumulate in significant concentrations in breast milk, and no data point to infant toxicity with their use.^{40,42,43} Castor oil and mineral oil should be avoided during breastfeeding.⁴⁰

Patient Factors

Laxative products are available in a wide array of oral dosage forms, which may be useful to improve acceptability of laxatives. The glucose and calorie contents of laxatives available as chewing gum, wafers, gummy candy, or chocolate tablets should be considered in patients with diabetes or calorie restrictions.

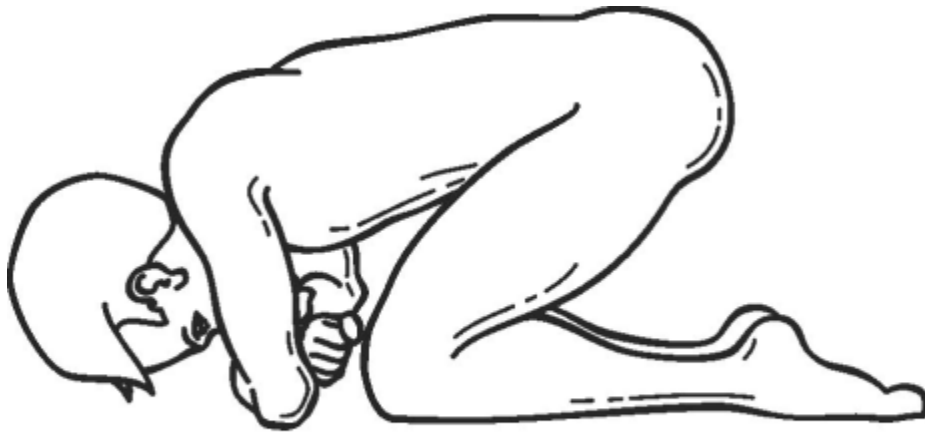
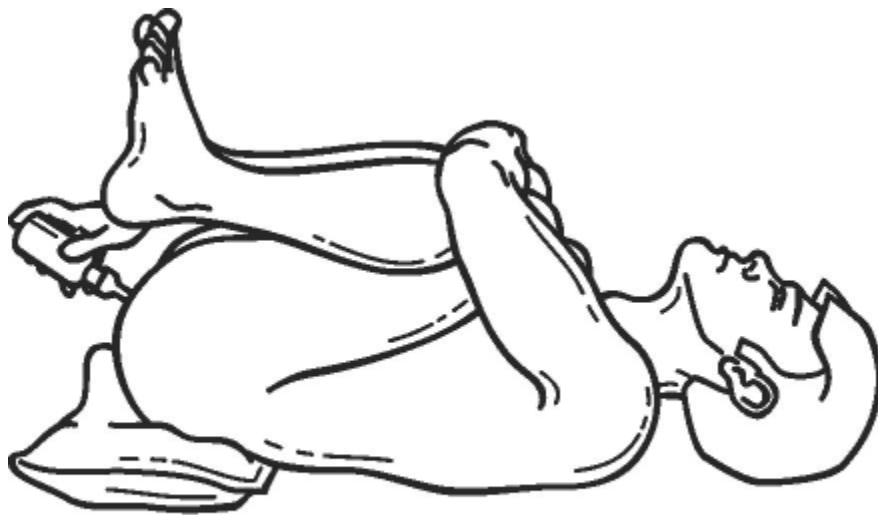
Patients with fluid restrictions should avoid use of bulk-forming laxatives. Patients on sodium-restricted diets should ascertain the sodium content of laxative products (especially saline laxatives) to avoid ingesting additional sodium.⁴⁴ Patients with severely limited mobility (e.g., postoperative patients, older adults) are at increased risk for constipation and may require regular use of stool softeners or laxative products to promote laxation.

Enemas are used routinely to prepare patients for surgery, obstetric delivery, and GI radiologic or endoscopic examinations. The mechanism of laxation with enemas varies by agent. Vegetable oil enemas lubricate and soften fecal matter, whereas tap water, normal saline, and sodium phosphate enemas have osmotic effects. Sodium phosphate enemas are more efficient and effective than tap water, soapsuds, saline, or vegetable oil enemas. When properly administered ([Table 15–7](#)), enemas clean only the distal colon. Improper use or administration may result in adverse effects (e.g., mucosal changes, spasm of the intestinal wall, colonic perforation).

Table 15–7 Administration of Enemas and Rectal Suppositories

Enemas	Suppositories
1. If someone else is administering the enema, lie on your left side with knees bent or assume the knee-to-chest position (drawings A and B, respectively). The	1. Gently squeeze the suppository to determine if it is firm enough to insert. Chill a soft suppository by placing it in the

Enemas	Suppositories
side-lying position (drawing A) is preferred for children younger than 2 years. If self-administering the enema, lie on your back with knees bent and buttocks raised (drawing C). A pillow may be placed under the buttocks.	refrigerator for a few minutes, or by holding it under cool running water.
2. If using a concentrated enema solution, dilute solution according to the product instructions. Prepare 1 pint (500 mL) for adults or ½ pint (250 mL) for children.	2. Remove the suppository from its wrapping.
3. Lubricate the enema tip with petroleum jelly or other nonmedicated ointment/cream. Apply the lubricant to the anal area as well.	3. Dip the suppository in lukewarm water for a few seconds to soften the exterior.
4. Gently insert the enema tip 2 inches (recommended depth for children) to 3 inches into the rectum.	4. Lie on your left side with knees bent or assume the knee-to-chest position (drawings A and B). The side-lying position (drawing A) is best for self-administration of a suppository. Small children can be held in a crawling position.
5. Allow the solution to flow into the rectum slowly. If you experience discomfort, the flow is probably too fast.	5. To ease insertion, relax the buttocks just before inserting the suppository. Gently insert the tapered end of the suppository high into the rectum. If the suppository slips out, it was not inserted past the anal sphincter (the muscle that keeps the rectum closed). In this case, reinsert the suppository correctly.
6. Retain the enema solution until the urge to evacuate is strong (usually 1–5 minutes).	6. Continue to lie down for a few minutes while holding the buttocks together, to allow the suppository to dissolve in the rectum. (For suppository administration in a child, the parent/caregiver may have to gently hold the buttocks closed.)
	7. Try to avoid a bowel movement for up to 1 hour after insertion of the suppository so that maximum intended action can occur.

Enemas**Suppositories****A****B****C**

Suppositories containing bisacodyl are used for postoperative and antepartum and postpartum care and are adequate in preparing for proctosigmoidoscopy. Glycerin suppositories are useful in initiating the defecation reflex in children and in promoting rectal emptying in adults.

Those patients who are allergic to gluten, wheat, milk or milk protein, or soy should be encouraged to review the inactive ingredient sections of the product packaging before selecting a specific agent. If it cannot be determined if the product contains such ingredients, the manufacturer can be contacted at the phone number on the packaging.

Patient Preferences

Palatability and convenience are important considerations with laxative products. Liquid formulations of emollients may be made more palatable if mixed with juices or milk. Mixing gritty, bulk-forming laxative powders (e.g., psyllium) with orange juice instead of water may increase their taste and texture palatability. Patients also may prefer wafer or “single-serving” packets of bulk-forming laxative powders for convenience and ease of use. Patients should be reminded that many fiber products marketed as grit-free, flavor-free, or taste-free may contain ingredients that have not been studied as bulk-forming laxatives and are approved only as dietary supplements (e.g., inulin). Most laxative ingredients are available in some form as generic products. However, patients with a specific desired dosage form or other preference may need to choose a brand-name product.

Complementary Therapies

Dietary supplements commonly used to treat constipation include flaxseed, aloe, cascara, and probiotics.⁴⁵ Evidence supporting the safety and efficacy of these products varies in extent and quality. A single double-blind trial demonstrated the superiority of flaxseed over psyllium in decreasing constipation, bloating, and abdominal pain over a 3-month period in patients with irritable bowel syndrome. However, a much larger body of evidence supports psyllium’s effectiveness, and practitioners should not recommend flaxseed on the basis of limited efficacy and safety data.⁴⁵

Although many commercially available stimulant laxatives are derived from

plants, patients should be advised to choose FDA-approved products if a stimulant laxative is indicated. FDA has banned the use of aloe and cascara in nonprescription stimulant laxatives, and both agents are classified as generally unsafe and not effective. Senna is available in dietary supplement form, but use of standardized, FDA-approved senna drug products is preferred.

Probiotics are thought to work in constipation through alteration of GI flora, stimulation of motility and peristalsis, and/or acceleration of gut transit.^{5,46} However, limited safety and efficacy evidence are available on probiotics in constipation, and these agents should be considered investigational for treatment of constipation at present (see also [Chapter 20](#)).^{5,46,47}

Assessment of Constipation: A Case-Based Approach

In the initial patient interview, the health care provider should obtain as much lifestyle and medical information as possible before making any recommendations for preventing or treating constipation. Appropriate information allows the provider to make rational recommendations that are based on knowledge of the patient, the clinical problem, and available products, as well as on the provider's own judgment and experience. A patient who presents with constipation should initially be evaluated for any signs of significant GI problems that may warrant medical evaluation or in which laxative use is inappropriate ([Figure 15–2](#)). Initial assessment should include questions about diet, fluid intake, physical activity, and any underlying pathologic conditions that may produce constipation as a symptom.

Also essential is information about the patient's bowel movements, including the caliber, color, and texture of stools, as well as frequency of elimination, along with use of any other medications or natural products and previous laxative use. For patients without a history of constipation, more in-depth evaluation is needed to determine whether an acute case of constipation resulted from new or old disease or from the use of medications. When information is insufficient to assess the cause of the symptoms, or if any doubt exists regarding the patient's disease status, medical referral is appropriate. Cases 15–1 and 15–2 provide sample assessments for two different patients presenting with constipation.

A Word About Opioid-Induced Constipation

Opioid use is common in the treatment of noncancer and cancer pain. Constipation is experienced by approximately 40% of patients taking opioid drugs and is the most common adverse effect with use of these agents. Opioid-induced constipation may prevent patients from receiving appropriate pain-relieving dosages or may lead to discontinuation of therapy despite the need for pain relief. Opioids cause constipation by binding to bowel and central nervous system receptors to decrease GI motility and intestinal secretions, leading to longer retention time of fecal matter in the intestines with consequent drying of the stool. Unlike with other opioid-induced adverse effects, patients generally do not develop tolerance to these constipating effects over time. Constipating effects of opioids are dependent on the drug dose and duration of use.^{19,24} Oral opioids generally are more constipating than parenteral agents. Transdermal fentanyl patches are less constipating than oral opioids and may be an option for outpatients requiring chronic opioid therapy.^{11,24}

Patients on a chronic opioid regimen will require a long-term laxative regimen to prevent and/or treat constipation. Stimulant laxatives (e.g., senna or bisacodyl, with or without docusate) are most commonly recommended.²⁴ Typically, a stool softener alone is not effective. Polyethylene glycol preparations or other osmotic agents also may be used for prevention and treatment of opioid-induced constipation. Saline laxatives or rectally administered preparations may be needed intermittently for acute evacuation, but not for long-term management. Bulk-forming laxatives are unlikely to be adequately effective if used alone and may not be tolerated because of fluid restrictions or immobility in some patients on chronic opioid therapy (e.g., those under palliative care).^{19,24}

Identify patients at risk for opioid-induced constipation to help prevent problems, and provide counseling about nondrug preventive measures. Educate patients to determine when the pain is not severe and a different pain medication could be used that does not cause constipation. For patients on chronic opioid therapy, emphasize the importance of bowel

regimen adherence, and explain the need for long-term laxative therapy with chronic opioid use. If appropriate, suggest alternative opioids (e.g., transdermal fentanyl) that may be less constipating. Educate patients on short-term opioid therapy about constipation, especially those with other risk factors for constipation (e.g., recent abdominal surgery or childbirth).

A Word About Laxative Overuse

Identify patients at risk for laxative overuse, such as those who do not have symptoms of constipation but inappropriately take laxatives frequently to achieve regular bowel movements (e.g., daily) or a softer stool consistency. Other patients may desire to “detoxify the system” with colon-cleansing regimens that contain laxatives.²⁸ Factors that contribute to laxative overuse include older age, misconceptions about normal bowel movement frequency, fear of constipation, and presence of comorbid conditions (e.g., eating disorders).^{29,30}

Excessive use of laxatives can cause acute-onset episodes of diarrhea and vomiting, fluid and electrolyte losses (especially hypokalemia), and dehydration. Concerns about long-term consequences of chronic stimulant laxative use have been disproved in the literature. Although earlier reports pointed to adverse effects associated with chronic use of stimulant laxatives, recent well-designed clinical trials do not support an increased risk of colonic muscle or nerve damage or colorectal cancer with use of these laxatives.^{30,31}

On the other hand, acute adverse effects have been recognized as a potential risk in patients who take large doses of laxatives for purging, colon cleansing, or detoxification purposes. Colon-cleansing preparations are available in many pharmacies and are promoted for a wide range of potential benefits, including removing toxins, losing weight, and preventing disease. No data have emerged to support these claims, and

acute overuse of colon-cleansing regimens can cause serious adverse effects. Unwarranted enemas, colonic irrigation, and “colon hydrotherapy” carry additional risks (e.g., bowel perforation or infection) and are not recommended.²⁸ If laxative overuse for purging related to anorexia or bulimia is suspected, medical referral for appropriate care is needed.

Educate patients whose misperceptions about the need for a daily bowel movement contribute to unnecessary laxative use. Explain to patients that normal bowel patterns vary and that daily bowel movements are not a physical necessity. Encourage lifestyle changes that can promote regularity, such as increased fluid intake, fiber intake, and physical activity.³⁰

Note that chronic laxative use may be appropriate in some patients (e.g., those on a chronic opioid regimen). A thorough medical history can help determine if laxative use and choice of agent are appropriate in individual cases.

Case 15–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient’s symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	A mother seeks advice regarding her preschool-age daughter, who has been constipated for the past 10 days. The child has not been able to pass any stool despite repeated straining. Her abdomen also is bloated, and she is “cranky.” She is not interested in eating because of feeling “full.”

Relevant Evaluation Criteria	Scenario/Model Outcome
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	The child recently started preschool and is eating new foods during the day.
c. Description of the patient's or caregiver's efforts to relieve the symptoms	The mother has been giving her daughter prune juice for the last 3 days.
d. Patient's identity	Allison Carter
e. Patient's age, gender, height, and weight	4 years, female, 3 ft 4 in., 40 lb
f. Patient's occupation	n/a
g. Patient's dietary habits	Eats pasta, pizza, chicken nuggets, and occasional fruit.
h. Patient's sleep habits	10 hours
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	None
j. Allergies	None
k. History of other adverse reactions to medications	None
l. Other (describe) -----	Allison typically has 2-3 bowel movements per day.
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the	The patient is experiencing constipation, most likely precipitated by the change in her routine and environment and her consumption of different foods during the day. Also, her regular

Relevant Evaluation Criteria	Scenario/Model Outcome
patient's primary problem(s).	diet at home lacks sufficient fiber. Constipation in children is common with a change in routine and/or environment.
3. Identify exclusions for self-treatment (Figure 15-2).	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer the patient to her pediatrician or other appropriate health care provider. (2) Recommend nondrug measures a. Institute a balanced diet with adequate fiber, fruits, and vegetables. b. At a minimum, drink fruit juices with sorbitol, which increases risk of diarrhea. c. Establish a regular stooling time for toilet-trained children (usually after a morning meal), and develop a supportive system (e.g., charts, stickers) for positively reinforcing bowel movements. d. Recommend strategies to prevent future recurrences of constipation. (3) Recommend docusate sodium 50–150 mg daily in single or divided doses to help facilitate resolution of symptoms. (4) Recommend a pediatric glycerin suppository. The glycerin suppository will offer the fastest resolution if the parent is able and willing to use that dosage form. (5) Recommend magnesium hydroxide chewable tablet 311 mg (2 tablets) or 400 mg (1–2 tablets) at bedtime daily to help facilitate resolution of symptoms. (6) For resolution of the symptoms, recommend senna 8.6 mg sennosides (½ tablet), senna liquid pod concentrate pediatric formulation 5 mL or 10 mL, or liquid sennosides 3.75 mL (2.5–3.75 mL) once daily. A

Relevant Evaluation Criteria	Scenario/Model Outcome
	stimulant laxative also will offer fast relief of symptoms. (7) Recommend self-care measures until the patient can see an appropriate health care provider. (8) Refer the patient to an appropriate health care provider if the therapeutic option and lifestyle changes do not alleviate symptoms within a week or if symptoms worsen with progression to self-care exclusions. (9) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	For fast relief of Allison's symptoms, she should be given a stimulant laxative, and Mrs. Carter should institute the recommended nondrug measures.
6. Describe the recommended therapeutic approach to the patient or caregiver.	Mrs. Carter should administer senna pediatric liquid concentrate formulation 5 mL (use the supplied measuring cup) once daily for resolution of Allison's symptoms. The medication usually takes effect in about 6–10 hours.
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"The senna liquid concentrate pediatric formulation will provide quick relief within 6–10 hours. Once your child has become used to her new routine and environment, the constipation will most likely resolve. However, it is important to continue a healthy diet with fruits, vegetables, and fiber. It also may be helpful to establish a regular stooling time for toilet-trained children (usually after a morning meal) and to develop a supportive system (e.g., charts or stickers) for positively reinforcing bowel movements."
Implement	
8. When recommending self-care with	"For most patients, carefully following the product instructions and the self-care measures listed here will help achieve these

Relevant Evaluation Criteria	Scenario/Model Outcome
nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	goals.”
a. Appropriate dose and frequency of administration	“Read and carefully follow labeled dosage and administration instructions for all laxative products.”
b. Maximum number of days the therapy should be employed	“If symptoms continue after 7 days of laxative treatment, contact your health care provider.”
c. Product administration procedures	“Oral laxatives are available as tablets, capsules, thin-film strips, chewing gum, wafers, effervescent granules, gummy candy, chocolate tablets, and other forms. Choose the best form for you.”
d. Expected time to onset of relief	“The medication should take effect in 6 to 10 hours.”
e. Degree of relief that can be reasonably expected	“The constipation symptoms should be relieved.”
f. Most common adverse effects	“The most common adverse effects of laxatives are abdominal cramping, gas, bloating, and diarrhea.”
g. Adverse effects that warrant medical intervention should they occur	“Patients—who fail to achieve a therapeutic response after 7 days of self-treatment require medical referral. See Figure 15-2 and the box ‘Patient Education for Constipation’ for additional information.”
h. Patient options in the event that condition worsens or persists	“If constipation symptoms continue after 7 days of laxative treatment, contact your health care provider.”
i. Product storage requirements	“Store the medication in a cool, dry place out of children’s reach.”
j. Specific nondrug measures	“To promote regular bowel movements, use nondrug strategies such as initiation of a high-fiber diet (slowly increase intake to 25–35 g/day), intake of plenty of fluids, and regular exercise.”

Relevant Evaluation Criteria	Scenario/Model Outcome
Solicit follow-up questions from the patient or caregiver.	"Can the liquid laxative be mixed in fruit juice or milk to make it easier to give to my daughter?"
Answer the patient's or caregiver's questions.	"No—the senna liquid concentrate pediatric formulation has a root beer flavor to make it easier to administer to children."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Ask Mrs. Carter to call to update you on Allison's response to your recommendations. Alternatively, you could call her in a few days to evaluate the outcome.

Case 15–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient says that she is having a very difficult time passing stool. She reports straining to pass "normal-looking" but soft stools. She has been having only about 1 bowel movement per week and is feeling bloated. She has been experiencing these symptoms for the past month.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Patient notes that her problem really started when she broke her ankle in a bicycle accident and then began taking a pain medication prescribed by her regular health care provider.
c. Description of the patient's efforts to relieve the symptoms	The patient has been using a stool softener for the past 2 weeks.

d. Patient's identity	Margaret Thomas
e. Age, gender, height, and weight	30 years, female, 5 ft 7 in., 150 lb
f. Patient's occupation	Works in an office for a nonprofit organization.
g. Patient's dietary habits	Usual diet consists of lots of vegetables and salad, pastas, occasional whole-grain breads, meat and fish, caffeinated coffee, diet sodas, and desserts.
h. Patient's sleep habits	Sleeps about 8 hours per night.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Vicodin (hydrocodone 7.5 mg/acetaminophen 325 mg) 1 tablet every 6 hours for pain; docusate 100 mg daily; multivitamin with iron
j. Allergies	None
k. History of other adverse reactions to medications	None
l. Other (describe) _____	Before her ankle injury, she typically had 3–4 bowel movements every week. She takes about 4 Vicodin tablets per day.

Assess

2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Ms. Thomas recently started taking an opioid medication, Vicodin, which can cause constipation. The patient's constipation appears to be correlated with the start of this medication. She also takes a multivitamin with iron, which can contribute to constipation.
3. Identify exclusions for self-treatment (Figure 15–2).	Unexplained changes in bowel habits; bowel symptoms that persist for more than 2 weeks.
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer the patient to an appropriate health care provider. (2) Recommend self-care with a nonprescription laxative and nondrug measures.

	(3) Recommend self-care until the patient can see an appropriate health care provider. (4) Refer the patient to an appropriate health care provider if the selected therapeutic option and lifestyle changes do not alleviate symptoms within 1 week. (5) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Ms. Thomas has experienced constipation secondary to the initiation of an opioid medication. She has been experiencing constipation-related symptoms for 1 month. She should consult an appropriate health care provider. However, she also should implement nondrug measures to help prevent constipation and to promote a healthy lifestyle.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"You should consult a health care provider since these symptoms have been going on for a month. You also should modify your diet to include more fiber, fruits, and vegetables. You should add a fiber supplement to your diet, and you should increase your fluid intake. Also, you should establish a regular exercise routine once your ankle is healed."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"This option is best because your constipation began after you started your new pain medication, and it has been occurring for a month. Therefore, nonprescription laxative therapy may not be the best choice right now. You should be evaluated by your health care provider."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	"Even though you need to see your health care provider, you can still implement nondrug measures that promote a healthy lifestyle, such as eating more fiber, fruits, and vegetables, and beginning a regular exercise routine when your ankle is healed. You should consult your health care provider about these measures as well."

Solicit follow-up questions from the patient or caregiver.	“Should I stop taking my pain medication?”
Answer the patient’s or caregiver’s questions.	“I would discuss this with your primary care provider. It may be time to decrease or stop your pain medication, especially if you are not experiencing severe pain. Your primary care provider also may be able to prescribe a different pain medication that does not cause constipation.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact the patient in 1-2 days to ensure that she made an appointment for further medical care.

Patient Counseling for Constipation

Patient education about laxative products is important for all patients (particularly for children and their caregivers and older adults). Before recommending a laxative product, health care providers should inform the patient of available nondrug measures, including information on proper diet, adequate fluid intake, and reasonable exercise. If a laxative is needed, the provider should explain why a particular type of laxative is appropriate for the present situation, how to use the laxative, when to expect results, what adverse effects could occur, and what precautions to take. The box “Patient Education for Constipation” lists specific information to include in patient counseling.

Evaluation of Patient Outcomes for Constipation

Once therapy has been selected, treatment effectiveness is determined by how rapidly constipation is relieved and to what degree normal bowel habits have been restored. With acute constipation, dietary changes, exercise, or bulk-forming laxatives may take several days to weeks to provide relief. Most

hyperosmotic, saline, or stimulant laxatives will provide relief within 3–72 hours. Enemas can produce evacuation within minutes. If initial treatment of constipation is ineffective, therapy should be repeated according to product-specific directions.

If an adequate response is not achieved after a short period of laxative use (usually within 7 days), assessment of whether the patient needs medical referral is indicated at the follow-up contact. If a laxative must be continued for an extended period, the patient should be referred for further evaluation, because the need for frequent use may be a sign of (1) a more severe form of constipation, (2) a medication adverse effect, or (3) an underlying medical problem.

Patient Education for Constipation

The primary goals of treatment are (1) to relieve constipation and reestablish normal bowel function, (2) to establish dietary and exercise habits to help prevent recurrence, and (3) to promote the safe and effective use of laxative products if needed. For most patients, carefully following the product instructions and the self-care measures listed here will help achieve these goals.

Nondrug Measures

- To promote regular bowel movements, use nondrug strategies such as initiation of a high-fiber diet (slowly increase intake to 25–35 g/day), intake of plenty of fluids, and regular exercise.
- Increase dietary fiber by eating foods with whole grains, oats, fruits, and vegetables.
- Avoid constipating foods, such as processed cheeses and concentrated sweets.
- Drink plenty of fluids (six to eight 8-ounce glasses a day) to help soften stool and move food through the GI tract.
- Develop and maintain a routine exercise program. Walking can be helpful if your heart is healthy and if you have no other apparent health risks.

- Establish a regular pattern for bathroom visits. Do not delay in responding to the urge to use the toilet; allow adequate time for elimination in a relaxed, unhurried atmosphere.
- Maintain general emotional well-being and avoid stressful situations.

Nonprescription Medications

- Bulk-forming laxatives (e.g., methylcellulose, psyllium)
- Hyperosmotic laxatives (e.g., polyethylene glycol [PEG] 3350, glycerin)
- Emollient laxatives, or “stool softeners” (e.g., docusate sodium)
- Lubricant laxative (mineral oil)
- Saline laxatives (e.g., magnesium citrate, magnesium hydroxide)
- Stimulant laxatives (e.g., bisacodyl, senna)

Complementary Therapies

- Not routinely recommended for self-treatment of constipation

Disease Information

- Constipation usually is defined as having fewer than 3 bowel movements per week that involve straining and the difficult passage of dry, hard stools. In most cases, constipation is temporary. Self-treatment for constipation is safe for short-term symptoms in patients without other underlying disorders or conditions.
- You do not need to take laxatives routinely if your bowel habits are interrupted for 1 or 2 days, nor do you need to routinely “clean your system.”

Drug Information

Bulk-Forming Laxatives

- Unless a rapid effect is needed (e.g., to clean out the bowel before a diagnostic endoscopic procedure or x-ray study), take a bulk-forming laxative. Be sure to drink at least 8 ounces of fluid with

each dose to prevent an intestinal blockage. If you have swallowing difficulties, alert your health care provider before taking a bulk-forming laxative.

- If you have diabetes or are on a carbohydrate- or calorie-restricted diet, choose sugar-free bulk-forming agents, if possible. Many bulk-forming agents contain sugar and have a high caloric content per dose.
- Do not give sugar-free bulk-forming products to patients with phenylketonuria.

Hyperosmotic Laxatives

- If you have irritable bowel syndrome, do not take PEG 3350 without the supervision of your primary care provider.
- When using PEG 3350, use the provided cap to measure the dose, or use 1 packet of powder of “single-serving” products. Mix the powder with 4–8 ounces of a hot, cold, or room-temperature beverage (e.g., water, juice, soda, coffee, tea).
- Consult a primary care provider before using glycerin suppositories if you have previously had a condition that caused rectal irritation.

Emollient Laxatives

- Do not take docusate if you are taking mineral oil unless told to do so by a primary care provider. Taking these together can increase the amount of mineral oil that gets into your body.

Lubricant Laxative

- Although some patients use mineral oil for occasional bouts of constipation, its use in self-care is strongly discouraged because safer agents that work just as well are available.
- Do not give mineral oil to children younger than 6 years, pregnant women, older adults, or immobile patients without the supervision of a primary care provider. These patients are at a higher risk for adverse effects from mineral oil.
- Do not take mineral oil with emollient laxatives (e.g., docusate). Taking these together can increase the amount of mineral oil that

gets into your body.

- To avoid impairing or delaying the absorption of foods, nutrients, and vitamins, do not take mineral oil within 2 hours of eating.
- Stop use and consult your health care provider if anal leakage of oil occurs. This adverse effect may indicate that your dose is too high.

Saline Laxatives

- Take doses with an 8-ounce glass of water, if possible, to prevent dehydration.
- Consult your health care provider before using a saline laxative if you are taking a diuretic (“water pill”) for high blood pressure (e.g., hydrochlorothiazide, furosemide), if you are taking other drugs that can cause electrolyte changes, or if you are on a sodium-, phosphate-, or magnesium-restricted diet.
- If you are an older adult, you may be at increased risk for dehydration or electrolyte imbalances with use of saline laxatives. Consult a health care provider before using these agents.
- Do not use magnesium sulfate (Epsom salt) to treat constipation except under the advice of a primary care provider.

Stimulant Laxatives

- Do not use castor oil to treat constipation except under the advice of a health care provider.
- Do not chew or crush bisacodyl tablets, which may cause stomach discomfort, fainting, and cramps. Do not use bisacodyl within 1 hour after taking an antacid or milk. Doing so can cause the tablet’s coating to break down too quickly.

Administration of Medication/Safe Usage

- Read and carefully follow labeled dosage and administration instructions for all laxative products.
- Oral laxatives are available as tablets, capsules, thin-film strips, chewing gum, wafers, effervescent granules, gummy candy, chocolate tablets, and other forms. Choose the best form for you, and consider glucose and caloric content if you have diabetes or

calorie restrictions.

- Rectal laxatives (enemas, suppositories) should be used according to administration instructions ([Table 15–6](#)).
- If constipation symptoms continue after 7 days of laxative treatment, contact your health care provider.
- Do not give laxatives to children younger than 2 years unless their use is recommended by a primary care provider.
- Take most laxatives at bedtime, especially if more than 6–8 hours will be needed to produce results.
- Do not take any laxatives at doses higher than the recommended amounts.

Warning Signs/Symptoms

- Do not take laxatives if you have marked abdominal pain, nausea, vomiting, significant abdominal distention, cramping, or fever—any of these may be evidence of a more serious condition (e.g., appendicitis).
- Do not take laxatives if you have a sudden change in bowel habits that persists for longer than 2 weeks, because such changes can be a sign of a more serious condition. See your primary care provider for treatment recommendations.
- With any rectal bleeding, presence of blood in your stool, or passage of black, tarry stools, see your health care provider. These may be signs of an underlying medical condition.
- If you have kidney or liver disease, heart failure, hypertension, or other conditions requiring sodium, potassium, magnesium, or calcium restriction, do not use laxative products with a maximum daily dose of more than 345 mg (15 mEq) sodium, 975 mg (25 mEq) potassium, 600 mg (50 mEq) magnesium, or 1800 mg (90 mEq) calcium.
- Consult your health care provider before using laxatives if you currently have or have a history of any condition that may affect self-treatment for constipation (e.g., paraplegia or quadriplegia, inflammatory bowel disease, colostomy, megacolon, ileostomy).
- Some laxatives require you to drink a lot of water with each dose. Patients with fluid restrictions should avoid bulk-forming or other

laxatives that require abundant fluid intake.

Adverse Effects

- The most common adverse effects of laxatives are abdominal cramping, gas, bloating, and diarrhea.

Interactions

- Avoid taking laxatives within 2 hours of ingestion of other medications.
- To make sure you avoid any potential drug–drug interactions, alert your health care provider if you are taking anticoagulants (blood thinners), digoxin (a heart medicine), sodium polystyrene sulfonate (an agent for treatment for high potassium levels), or other drugs that need to be maintained at precise levels.

Storage of Medications/Expiration Date/Signs of Instability

- Discard any medications that are outdated, that appear to have been tampered with, or that have an unusual appearance.

Key Points for Constipation

- Nonprescription laxative treatment should not be recommended if exclusion criteria for self-treatment are present ([Figure 15–2](#)). Patients in whom such exclusions are identified require medical referral.
- Special circumstances and patient characteristics (e.g., pregnancy, advanced age) should be considered in assessing the need for self-medication.
- For most cases of simple constipation, a balanced diet, exercise, and adequate fluid intake are helpful.

- Bulk-forming laxatives and PEG 3350 taken as directed are first-line choices for most adults with constipation, but they may take up to 72 hours to work. Glycerin suppositories or stimulant laxatives provide faster relief, if needed.
- Therapy with any laxative product should be limited to 7 days, unless supervised by a health care provider.
- If rectal bleeding occurs at any time during use of a laxative, or if constipation persists despite therapy, patients should stop using the laxative and consult a health care provider.¹⁵
- To reduce the potential for drug interactions, patients should avoid taking most laxatives within 2 hours of ingestion of other medications.

Chapter 16: Diarrhea

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Diarrhea is a gastrointestinal (GI) disturbance characterized by an abnormal increase in stool frequency, liquidity, weight (greater than 200 g per 24 hours), or volume (200 mL per 24 hours).¹ Although the “normal” frequency of bowel movements varies with individual physiology, more than 3 bowel movements per day is considered abnormal.

Diarrhea may be acute, persistent, or chronic. *Acute* diarrhea, defined as presence of symptoms for fewer than 14 days, generally can be managed with fluid and electrolyte replacement, dietary interventions, and nonprescription drug treatment. In *persistent* diarrhea, symptoms last 14 days to 4 weeks. *Chronic* diarrhea, by definition, lasts more than 4 weeks. Chronic and persistent diarrheal illnesses often are secondary to other chronic medical conditions or treatments and necessitate medical care, so these illnesses are not considered in this chapter.

Worldwide, 2.4 billion episodes of acute diarrhea occur annually, making diarrhea a significant contributor to morbidity and mortality, especially for children younger than 5 years of age, in whom it causes 500,000 deaths each year.² The overall monthly prevalence of acute gastroenteritis (an irritation of the GI tract commonly caused by viruses or bacteria that often results in diarrhea) in the United States is 8.3%, with an annual incidence of approximately 1 episode per person per year.³ Prevalence rates are highest in children younger than 5 years of age and lowest in older adults (i.e., 65 years of age and older). Most patients experiencing diarrheal illness do not seek medical attention. However, in the United States, acute gastroenteritis and its complications result in 600,000 hospitalizations and 5,000 deaths, with an estimated cost of \$145 billion each year.³

Pathophysiology of Diarrhea

Table 16–1 highlights some of the common viral, bacterial, and protozoal infections associated with diarrhea and their treatment. Epidemiologic factors that increase the risk for particular infectious diarrheal diseases or their spread

include attendance or employment at daycare centers, occupation as a food handler or caregiver, congregate living conditions (e.g., nursing homes, prisons, multifamily dwellings), consumption of unsafe foods (e.g., raw or undercooked meat, eggs, shellfish), and presence of medical conditions such as acquired immunodeficiency syndrome (AIDS) or diverticulitis. Acute diarrhea also may be caused by poisoning, medications, intolerance of certain foods, or various non-GI acute or chronic illnesses. [Table 16–2](#) lists selected medications that may cause diarrhea.

Table 16–1 Common Infectious Diarrheas and Their Treatment

Type	Epidemiologic/ Etiologic Factors	Symptoms	Treatment	Usual Prognosis
Viral				
Rotavirus	Infects infants; oral-fecal spread	Onset at 24–48 hours after exposure; vomiting, fever, nausea, acute watery diarrhea	Vigorous fluid and electrolyte replacement	Self-limiting, usually lasts 5–8 days
Norovirus	Infects all ages; frequently spread person to person by the fecal–oral route; causes “24-hour stomach flu”	Onset at 24–48 hours after exposure; sudden-onset vomiting, nausea, headache, myalgia, fever, watery diarrhea	Fluid and electrolytes	Self-limiting, usually lasts 12–60 hours
Bacterial				
<i>Campylobacter jejuni</i>	Ingestion of contaminated food or water; oral-fecal spread; immunocompromised host	Onset at 24–72 hours after exposure; nausea, vomiting, headache,	Fluid and electrolytes; in severe or persistent diarrhea, antibiotics may be required ^a	Self-limiting, usually lasts <7 days

Type	Epidemiologic/ Etiologic Factors	Symptoms	Treatment	Usual Prognosis
		malaise, fever, watery diarrhea		
<i>Salmonella</i>	Ingestion of improperly cooked or refrigerated poultry and dairy products; immunocompromised host	Onset at 12–24 hours after exposure; diarrhea, fever, chills, malaise, myalgia, epigastric pain, anorexia	Fluid and electrolytes for mild cases; antibiotics reserved for complicated cases ^b	Self-limiting
<i>Shigella</i>	Ingestion of contaminated vegetables or water; frequently spread person to person; immunocompromised host	Onset at 24–48 hours after exposure; nausea, vomiting, diarrhea, (stool may contain blood or mucus), fever	Fluid and electrolytes; antibiotics ^c	Self-limiting, usually lasts <7 days
<i>Escherichia coli</i> (enterotoxigenic <i>E. coli</i> [ETEC], enteroaggregative <i>E. coli</i> [EAEC])	Ingestion of contaminated food or water; recent travel outside the United States or to a U.S. border area	Onset at 8–72 hours after exposure; watery diarrhea, fever, abdominal cramps, bloating, malaise, occasional vomiting	Fluid and electrolytes; antibiotics ^d	Self-limiting, usually within 3–5 days
Shiga toxin-producing <i>E. coli</i> (STEC), including <i>E. coli</i> O157:H7 and non- O157 strains	Ingestion of contaminated food or water; direct person- to-person spread	Onset at 8–72 hours after exposure; watery and often bloody diarrhea,	Fluid and electrolytes	Self-limiting, usually within 5–10 days

Type	Epidemiologic/ Etiologic Factors	Symptoms	Treatment	Usual Prognosis
		abdominal cramps, hemolytic uremic syndrome		
<i>Clostridioides difficile</i>	Antibiotic-associated diarrhea leading to pseudomembranous colitis	Onset during or up to several weeks after antibiotic therapy; watery or mucoid diarrhea, high fever, cramping	Fluid and electrolytes; discontinuation of offending agent; antibiotics	Self-limiting; tends to recur
<i>Clostridium perfringens</i>	Ingestion of contaminated food, especially meat and poultry	Onset at 8–14 hours after exposure; watery diarrhea without vomiting, cramping, mid-epigastric pain	Fluid and electrolytes	Self-limiting; usually resolves within 24 hours
<i>Staphylococcus aureus</i>	Ingestion of improperly cooked or stored food	Onset at 1–6 hours after exposure; nausea, vomiting, watery diarrhea	Fluid and electrolytes	Self-limiting
<i>Yersinia enterocolitica</i>	Ingestion of contaminated food	Onset within 16–48 hours of exposure; fever, abdominal pain, diarrhea, vomiting	Fluid and electrolytes; antibiotics may be needed in severe cases	Self-limiting, although diarrhea may persist for up to 3 weeks

Type	Epidemiologic/ Etiologic Factors	Symptoms	Treatment	Usual Prognosis
<i>Vibrio cholerae</i>	Ingestion of contaminated food, including undercooked or raw seafood; recent travel outside the United States	Onset within 24–48 hours of exposure; painless, watery, and often voluminous diarrhea, vomiting	Fluid and electrolytes; antibiotics needed in moderate to severe cases	Self-limiting, although severe, fatal illness may occur
<i>Bacillus cereus</i>	Ingestion of contaminated food	Onset within 10–12 hours of exposure; abdominal pain, watery diarrhea, tenesmus, nausea, vomiting	Fluid and electrolytes	Self-limiting
Protozoal				
<i>Giardia intestinalis</i>	Ingestion of water contaminated with human or animal feces; frequently spread person to person; immunocompromised host	Onset at 1–3 weeks after exposure; acute or chronic watery diarrhea, nausea, vomiting, anorexia, flatulence, abdominal bloating, epigastric pain	Fluids and electrolytes; antimicrobial therapy ^e	Resolves with treatment
<i>Cryptosporidium</i> spp.	Frequently spread person to person; travel outside the United States; AIDS, immunocompromised host	Onset at 2–14 days after exposure; acute or chronic watery diarrhea,	Fluid and electrolytes; antimicrobial therapy ^f	Self-limiting, lasting up to 3 weeks, except in patients with AIDS or other immunosuppressive diseases

Type	Epidemiologic/ Etiologic Factors	Symptoms	Treatment	Usual Prognosis
		abdominal pain, flatulence, malaise		
<i>Entamoeba histolytica</i>	Travel outside the United States; fecal-soiled food or water; immunocompromised host	Chronic watery diarrhea, abdominal pain, cramps	Fluid and electrolytes; antibiotics ^a	Good, except for immunocompromised host
<i>Isospora belli</i>	Ingestion of contaminated food or water; immunocompromised host	Onset at approximately 1 week after exposure; profuse watery diarrhea, malaise, anorexia, weight loss, abdominal cramps	Fluid and electrolytes; antibiotics	Self-limited, remitting in 2–3 weeks

^a Empiric therapy with prescription antibiotics (e.g., azithromycin, erythromycin) should be considered for patients with febrile diarrheal illness, especially if moderate to severe invasive disease is suspected, and for patients in whom supportive therapy fails to manage symptoms. Ciprofloxacin and doxycycline have been recommended but are no longer considered first-line agents because many *Campylobacter* strains are resistant to these antibiotics.

^b Antibiotics are not indicated routinely for *Salmonella* gastroenteritis; antibiotic therapy is used in infants and young children who fail to respond to supportive treatment, who do not spontaneously remit, or who are at increased risk of disseminated disease. Antibiotic therapy also is indicated for suspected bacteremia in patients at high risk for this complication. Such patients include those who appear to be toxic with high fever (temperature >102.2°F [39.0°C]); infants (<3 months); older adult patients (≥65 years); patients with cancer, immunodeficiency (e.g., AIDS), or hemoglobinopathy (e.g., sickle cell disease); immunocompromised persons (including transplant recipients and patients taking corticosteroids); patients who are on

hemodialysis; and patients with vascular grafts or prosthetic joints. Fluoroquinolones are used for adults if infection is *not* acquired in Asia; with Asia-acquired infections, azithromycin or ceftriaxone is recommended. Ceftriaxone is used for children. Duration of antimicrobial therapy is usually 7–14 days. Alternatively, azithromycin can be used for 5–7 days.

^c Antibiotic therapy should be reserved for immunocompromised patients or those with severe or complicated disease. A fluoroquinolone (ciprofloxacin, levofloxacin) or ceftriaxone is recommended for adults; azithromycin or ceftriaxone is recommended for children.

^d Antibiotic treatment with azithromycin, ceftriaxone, or rifaximin is given for moderate to severe traveler's diarrhea caused by *E. coli*; mild, self-limited infection usually can be managed symptomatically without antibiotics. Fluoroquinolones are no longer recommended as first-line agents in many regions of the world because of increasing resistance; trimethoprim–sulfamethoxazole is no longer recommended at all on account of resistance. Antibiotic treatment is not recommended for gastroenteritis caused by *E. coli* O157:H7, because such treatment is likely to enhance toxin release, which may increase risk for hemolytic uremic syndrome. Because antibiotic treatment of traveler's diarrhea also has been associated with increased risk for colonization by multidrug-resistant organisms, including extended-spectrum β -lactamase-producing and carbapenemase-producing strains of Enterobacteriaceae, single-dose regimens (azithromycin, fluoroquinolones) are equivalent to multidose regimens and may be more convenient for the traveler.³⁰ Adverse GI effects may limit use of single-dose azithromycin.

^e Self-treatment for giardiasis is not appropriate; tinidazole, metronidazole, and nitazoxanide are effective prescription alternatives for treating this condition.

^f Self-treatment for cryptosporidiosis is not appropriate. Nitazoxanide is the drug of choice for immunocompetent and human immunodeficiency virus (HIV)-negative patients. It is not approved for use in immunocompromised persons (including HIV-positive patients), in whom it is contraindicated; effective antiretroviral therapy is recommended as the best treatment for these patients.

^g Self-treatment for amebiasis is not appropriate; prescription therapy with metronidazole or tinidazole followed by either paromomycin or iodoquinol is preferred.

Key: AIDS = Acquired immunodeficiency syndrome; GI = gastrointestinal.

Source: Adapted from Riddle MS, DuPont HL, Connor BA. ACG clinical guideline:

diagnosis, treatment, and prevention of acute diarrheal infections in adults. *Am J Gastroenterol*. 2016;111(5):602–622; Antimicrobial therapy. Sanford Guide Web Edition 2019. Available at: <https://webedition.sanfordguide.com/en>. Accessed May 14, 2019; and American Academy of Pediatrics. *Red Book: 2018–2021 Report of the Committee on Infectious Diseases*. 31st ed. Available at: <https://redbook-solutions-aap-org.proxy.lib.umich.edu/>. Accessed May 14, 2019.

Table 16-2 Selected Drugs and Herbal Products That May Cause Diarrhea

ACE inhibitors (captopril, lisinopril)
Acetylcholinesterase inhibitors
Aloe vera
Alpha-glucosidase inhibitors ^a
Angiotensin II receptor blocker
Antibiotics ^b
Anticholinergic agents
Carbamazepine
Cholinergic agents ^b
Cimetidine
Colchicine ^a
Digitalis
Echinacea
Ginseng
Highly active antiretroviral therapy ^a
HMG-CoA reductase inhibitors
Magnesium-containing antacids
Metformin

Methyldopa
Misoprostol
NSAIDs
Orlistat ^b
Osmotic laxatives ^b
Prebiotics
Proton pump inhibitors
Ranitidine
Selective serotonin reuptake inhibitors ^b
St. John's wort
Stimulant laxatives (bisacodyl, senna)
Theophylline
Thyroid hormones
Ticlopidine ^b

^a ≥20% incidence of diarrhea.

^b ≥10% incidence of diarrhea.

Key: ACE = Angiotensin-converting enzyme; HMG-CoA = 5-hydroxy-3-methylglutaryl-coenzyme A; NSAIDs = nonsteroidal anti-inflammatory drugs.

Source: Adapted from Abraham B, Sellin JH. Drug-induced diarrhea. *Curr Gastroenterol Rep.* 2007;9:365–372; Philip NA, Ahmed A, Pitchumoni CS. Spectrum of drug-induced chronic diarrhea. *J Clin Gastroenterol.* 2017;51(2):111–117.

Viral Gastroenteritis

Noroviruses constitute the most common cause of diarrheal illness in adults and children, with the highest incidence in children younger than 5 years of

age. Noroviruses are responsible for 18% (or 685 million) of acute gastroenteritis infections occurring annually worldwide; one fifth of such infections in young children are caused by noroviruses. Globally, norovirus infection causes 212,000 deaths annually and imposes an economic burden of \$4.2 billion in direct health system costs and over \$60 billion in societal costs.⁴⁻⁷ Each year in the United States, noroviruses cause as many as 800 deaths, 71,000 hospitalizations, 400,000 emergency department visits, 1.9 million outpatient visits, and 21 million total illnesses.⁸

Norovirus gastroenteritis occurs year-round; in the United States, a seasonal peak of infection is seen each winter. The symptoms, clinical course, and treatment are described in [Table 16-1](#). Although most often transmitted by contaminated water or food, norovirus also can be transmitted from person to person and through contact with contaminated environmental surfaces. Outbreaks of infection frequently occur in health care institutions and long-term care facilities, on cruise ships and college campuses, and among military personnel and immunocompromised patients. Chronic norovirus infection is recognized as a significant risk in persons with compromised immune systems, who may experience symptomatic infection with chronic diarrhea for 4 weeks to 9 years.^{9,10}

Other viral causes of gastroenteritis include adenoviruses, astroviruses, enterovirus, hepatitis A virus, parechovirus, rotaviruses, and sapoviruses. Rotavirus causes gastroenteritis in patients of all ages; worldwide, it is the most common cause of severe diarrhea disease in infants and young children. Vaccines to prevent rotavirus gastroenteritis are available and are recommended for routine use in healthy infants. Vaccination rates among U.S. children 19–35 months of age range from 71% to 74% (for 2013 to 2017).¹¹ Despite this epidemiologically low vaccination rate, rotavirus is now detected in only about 3% of children with acute gastroenteritis.¹² Vaccination has lowered the burden of rotavirus disease significantly in the United States, reducing hospitalizations, emergency department visits, and outpatient visits.

Rotavirus tends to be a seasonal infection, with peaks of gastroenteritis occurring between November and February. It is spread by the fecal–oral route, can cause severe dehydration and electrolyte disturbances, and may result in death. Clinical features are presented in [Table 16-1](#).

Bacterial Gastroenteritis

Bacterial pathogens cause approximately 10% of acute diarrheal illnesses in the United States each year; most cases result from foodborne transmission.

Pathogens most commonly responsible, in order of decreasing causality, are *Campylobacter* spp.; *Salmonella* spp.; *Shigella* spp.; *Escherichia coli* (including O157:H7, non-O157:H7 Shiga toxin-producing *E. coli* [STEC], enterotoxigenic *E. coli* [ETEC], enteroaggregative *E. coli* [EAEC]), diffusely adherent *E. coli* [DAEC], and other diarrheagenic strains); *Clostridium* spp.; *Clostridioides difficile*; *Bacillus* spp.; *Staphylococcus* spp.; *Yersinia enterocolitica*; *Vibrio* spp.; and *Listeria* spp.^{13,14} In addition, *Aeromonas* spp., *Arcobacter* spp., enterotoxigenic *Bacteroides fragilis*, *Klebsiella oxytoca*, *Laribacter hongkongensis*, and *Plesiomonas shigelloides* also may cause acute diarrhea.

Bacteria cause diarrhea through elaboration of enterotoxin (e.g., ETEC, *Staphylococcus aureus*), by attachment and production of localized inflammatory changes in the gut (e.g., EAEC, enteropathogenic *E. coli*, STEC, *C. difficile*), or by directly invading the mucosal epithelial cells (e.g., *Shigella*, *Salmonella*, *Yersinia*, *Campylobacter jejuni*, invasive *E. coli*). Patients with diarrheal illness caused by toxin-producing pathogens have a watery diarrhea, with infection primarily involving the small intestine. If the large intestine is the primary site of infection, invasive organisms produce a dysentery-like (bloody diarrhea) syndrome characterized by fever, abdominal cramps, tenesmus (straining), and the frequent passage of small-volume stools that may contain blood and mucus. Clinical features of common bacterial diarrheas are presented in [Table 16–1](#).

Acute infectious gastroenteritis, most notably infection caused by *C. jejuni*, *Shigella*, *Salmonella*, diarrheagenic *E. coli*, norovirus, and *Giardia intestinalis*, is one of the strongest known risk factors for development of irritable bowel syndrome (IBS).¹⁵ Postinfection IBS develops in approximately 10% of patients with previous enteric infection and usually is diagnosed 1–2 years after an episode of acute gastroenteritis. The prognosis usually is favorable for most patients; IBS symptoms resolve 4–8 years after diagnosis.¹⁶ Acute gastroenteritis also may unmask or exacerbate underlying chronic GI disorders, such as celiac disease, Crohn disease, or ulcerative colitis.

Protozoal Diarrhea

Diarrhea also may be caused by protozoa, including *G. intestinalis*, *Entamoeba histolytica*, *Isospora belli*, and *Cryptosporidium* spp. Nonprescription therapies are not available to manage diarrhea caused by these pathogens, and self-management is inappropriate.

Foodborne Gastroenteritis

Foodborne transmission of pathogens causes 47.8 million episodes of acute gastroenteritis, more than 127,000 hospitalizations, and approximately 3000 deaths in the United States each year.¹⁷ When pathogens are identified, 59% of these infections are caused by viruses (predominantly noroviruses), 39% by bacteria, and 2% by protozoa.¹⁷ Recent surveillance statistics (all per 100,000 population) on the incidence of foodborne illnesses confirm that *Salmonella* and *Campylobacter*, which caused 15.45 and 13.45 cases of illness in 2012, respectively, are the most frequently diagnosed bacterial pathogens. These are followed by *Shigella* (5.81 cases), *Cryptosporidium* (2.44 cases per), STEC non-O157 (1.43 cases), STEC O157:H7 (0.92 case), *Vibrio* (0.45 case), *Yersinia* (0.28 case), and *Listeria* (0.24 case).¹⁸ Other causes of foodborne gastroenteritis include *Cyclospora cayetanensis* and rotavirus.

Outbreaks of foodborne bacterial infection have been traced to poor sanitation and manufacturing practices in food production facilities and contamination of foods in various community locations, such as grocery stores and restaurants. Outbreaks of infection also have been associated with specific foods listed in [Table 16–3](#). Accordingly, obtaining a thorough history of the patient’s food intake 48–72 hours before the onset of diarrhea is essential in identifying a possible cause.

Table 16–3 Specific Foods Associated With Foodborne Gastroenteritis	
Organism	Associated Foods
Shiga toxin-producing <i>Escherichia coli</i> (STEC), including <i>E. coli</i> O157:H7 and non-O157 strains	Apple cider, unpasteurized
	Bologna
	Clover sprouts, raw

Organism	Associated Foods
	Eggs
	Gouda cheese
	Ground beef (undercooked)
	Lettuce
	Milk, raw
	Cookie dough, raw, refrigerated prepackaged
	Spinach
<i>Salmonella</i>	Chicken
	Dry dog food ^a
	Eggs
	Ground beef
	Ground turkey
	Jalapeno peppers
	Mangoes
	Melons (e.g., cantaloupe)
	Papayas
	Peanut butter
	Pine nuts
	Pistachio nuts
	Red and black pepper spice
	Yellowfin tuna, raw, scraped, ground
<i>Campylobacter</i>	Milk
	Chicken

Organism	Associated Foods
<i>Listeria</i>	Cold cuts
	Hummus
	Melons
	Milk
	Ricotta cheese
	Soft cheeses
<i>Cyclospora</i>	Raspberries

^a *Salmonella* infection is a zoonotic disease—that is, the infection can be transmitted from animals to people, and people have acquired *Salmonella* infections after contact with contaminated dry pet food or with an animal that has eaten contaminated dry pet food. Spread is by the fecal–oral route.

Outbreaks of acute foodborne illness caused by *E. coli* O157:H7 and other STECs constitute a major public health issue. Toxins produced by these organisms cause an acute bloody diarrhea and may be associated with serious, potentially fatal systemic complications, such as hemolytic uremic syndrome or thrombotic thrombocytopenic purpura.

Traveler’s Diarrhea

Traveler’s diarrhea is an acute, secretory diarrhea (i.e., the pathogen or its toxin affects the ion transport processes of the epithelial cells, thereby stimulating the active secretion of electrolytes and water into the intestines).¹⁹ This type of diarrhea is acquired mainly through ingestion of food or water contaminated with bacterial enteropathogens. It is the most predictable and common travel-related illness, with rates as high as 70%, and most often is of bacterial origin.²⁰ Traveler’s diarrhea can be caused by (in decreasing order of frequency) ETEC, *C. jejuni*, *Shigella* spp., *Salmonella* spp., EAEC, and DAEC; viral pathogens (e.g., norovirus); or parasites (e.g., *Giardia* spp., *Cryptosporidium* spp., *Entamoeba* spp.).²¹ Other causative bacterial pathogens include *Shigella* spp., *Salmonella*

spp., *C. jejuni*, *Aeromonas* spp., *Plesiomonas* spp., enterotoxigenic *B. fragilis*, and non-cholera *Vibrio* spp. Causative pathogens often are found on fruits, vegetables, raw meat, and seafood, and even in hot sauces, as well as in local water, including ice cubes made from tap water. The diarrheal disorders caused by these organisms are characterized in [Table 16–1](#). Bacterial and viral pathogens have an incubation period of 6–72 hours and thus result in a quicker onset of diarrhea than that typical for protozoal pathogens. Protozoal pathogens generally have an incubation period of 1–2 weeks, with onset of diarrhea rarely seen in the first few days of travel. A potential exception is *Cyclospora cayetanensis*, for which diarrheal illness can manifest quickly in areas of high risk.²⁰ The characteristic course includes production of 3–8 (or more) watery stools per day, with symptoms usually subsiding over 3–7 days.

Food-Induced Diarrhea

Food intolerance can provoke diarrhea and may result from a food allergy or ingestion of foods that are excessively fatty or spicy or contain a high amount of dietary fiber or many seeds. Dietary carbohydrates (e.g., lactose, sucrose) normally are hydrolyzed to monosaccharides by the enzyme lactase. If not hydrolyzed, these carbohydrates pool in the lumen of the intestine, where they produce an osmotic imbalance. The resulting hyperosmolarity draws fluid into the intestinal lumen, causing diarrhea. Lactase activity may be reduced by infectious diarrhea; thus, acute viral diarrhea may cause temporary milk intolerance in patients of all ages. Lactase deficiency resulting from viral gastroenteritis is short-lived, but it is particularly problematic during the first few days of the disease. Infants born with lactase deficiency and adults who acquire lactase deficiency are intolerant of cow milk and milk-based products. Lactase enzyme products are effective treatments for some patients (see “Treatment of Diarrhea”).

Clinical Presentation of Diarrhea

The most common signs and symptoms of acute infectious diarrheal illnesses are shown in [Table 16–1](#). Variability in the causes of diarrhea makes identification of the pathophysiologic mechanisms difficult. The etiology, and subsequently the pathophysiology, can be determined by obtaining a thorough medical history in most cases. However, a complete medical

assessment, including clinical laboratory evaluation, may be required to identify the cause in a subset of patients with severe or persistent diarrhea.

Diarrhea can be classified as osmotic, secretory, inflammatory, or motor, depending on the underlying pathophysiologic mechanisms that disrupt normal intestinal function. The common mechanisms of acute diarrhea are osmotic and secretory, whereas motor and inflammatory mechanisms commonly underlie chronic diarrheal illnesses. **Table 16–4** correlates the clinical groups and mechanisms with their most common causes.

Table 16–4 Clinical Classification of Diarrhea

Type	Mechanism(s)	Common Causes
Osmotic	• Unabsorbed solutes in intestines increase luminal osmotic load, retarding fluid absorption. • Decreased absorption of solutes and fluid can be secondary to brush border damage caused by lactase deficiency or infection. • Viral-induced damage to epithelial cells accelerates migration of immature crypt cells to the tip of the villus; altered epithelial turnover also decreases absorption.	Infections: noroviruses, rotaviruses, <i>Escherichia coli</i> , <i>Campylobacter jejuni</i> ; lactase deficiency, excess magnesium antacid intake
Secretory	• Stimulation of crypt cells produces net flow of electrolytes and fluids into intestinal lumen. • Tumors can secrete GI hormones and peptides that act as secretagogues.	Infections: <i>C. jejuni</i> , <i>Clostridioides difficile</i> , <i>E. coli</i> , <i>Salmonella</i> , <i>Shigella</i> , <i>Vibrio</i> , rotaviruses, <i>Giardia intestinalis</i> , <i>Cryptosporidium</i> spp., <i>Isospora</i> ; ileal resection, thyroid cancer
Inflammatory	• Impaired fluid absorption and leaking of mucus, blood, and pus into lumen caused by	Infections: <i>C. jejuni</i> , <i>E. coli</i> , <i>Salmonella</i> , <i>Shigella</i> , <i>Yersinia</i> , <i>Entamoeba histolytica</i> ; ulcerative colitis, Crohn disease

Type	Mechanism(s)	Common Causes
	inflammation of intestinal mucosa (e.g., IBD) or bacterial infection (i.e., dysentery).	
Motor	Abnormally rapid intestinal transit time reduces contact time between luminal contents and absorptive areas of intestinal wall.	IBS, diabetic neuropathy

Key: GI = Gastrointestinal; IBD = inflammatory bowel disease; IBS = irritable bowel syndrome.

Bacterial enterotoxins play a role in the pathophysiology of secretory diarrheas. Enterotoxins elaborated by *E. coli* and *Vibrio cholerae* evoke the release of endogenous secretagogues that mediate secretory reflexes, including serotonin, substance P, and vasoactive intestinal peptide. Some enterotoxins, such as cholera toxin, can directly stimulate GI secretomotor neurons to increase intestinal secretion. *Clostridioides difficile* enterotoxin A also injures enterocytes and evokes a necroinflammatory response that causes a secretory diarrhea. Although viruses, such as rotavirus, also produce enterotoxins, the role of viral enterotoxins in the disease pathophysiology is uncertain. In addition, inflammatory mediators (e.g., interleukins 1 and 6, prostaglandins, substance P, tumor necrosis factor α , platelet-activating factor) evoked by enteric infection stimulate a characteristic GI motility pattern that leads to the urgent defecation associated with diarrhea and that causes abdominal cramps.

Stool characteristics give valuable information about the pathophysiology of the diarrheal illness. For example, undigested food particles in the stool suggest disease of the small intestine. Black, tarry stools may indicate upper GI bleeding, and red stools suggest possible lower bowel or hemorrhoidal bleeding or simply recent ingestion of red food (e.g., beets) or drug products

(e.g., rifampin). In secretory diarrhea of the small bowel, chloride secretion and inhibition of sodium absorption appear to be the major events; thus, stools will be high in sodium content. Passage of many small-volume stools suggests a colonic disorder. Yellowish stools may indicate the presence of bilirubin and potentially serious pathology of the liver. A whitish tint to the stool points to a fat malabsorption disease.

Fluid and electrolyte imbalance is the major complication of diarrheal illness. Therefore, assessment of the patient's risk for dehydration and the degree of dehydration present is key to determining the appropriateness of self-care and the need for medical referral. The specific signs and symptoms of dehydration correlate with the severity of the diarrhea, as well as the etiology and degree of fluid and electrolyte losses ([Table 16-5](#)).²²

Table 16-5 Assessment of Dehydration and Severity of Acute Diarrhea			
Assessment Feature	Self-Treatable		Not Self-Treatable
	Minimal or No Dehydration	Mild to Moderate Dehydration/Diarrhea	Severe Dehydration/Diarrhea
Degree of dehydration (% loss of body weight)	<3%	3%–9%	>9%
Signs of dehydration ^a			
Mental status	Good, alert	Normal, fatigued or restless, irritable	Apathetic, lethargic, unconscious
Thirst	Drinks normally, might refuse liquids	Thirsty, eager to drink	Drinks poorly, unable to drink
Heart rate	Normal	Normal to increased	Tachycardia, bradycardia in most severe cases

Assessment Feature	Self-Treatable		Not Self-Treatable
	Minimal or No Dehydration	Mild to Moderate Dehydration/Diarrhea	Severe Dehydration/Diarrhea
Quality of pulses	Normal	Normal to decreased	Weak, thready, impalpable
Breathing	Normal	Normal, fast	Deep
Eyes	Normal	Slightly sunken ^b	Deeply sunken ^b
Tears	Present	Decreased ^b	Absent
Mouth and tongue	Moist	Dry	Parched
Skin fold	Instant return (recoil) to normal on release	Recoil in <2 seconds	Recoil in >2 seconds
Capillary refill	Normal	Prolonged	Prolonged, minimal
Extremities	Warm	Cool	Cold, mottled, cyanotic
Urine output	Normal to decreased	Decreased ^b	Minimal ^b
Number of unformed stools/day	<3	3–5	6–9
Other signs/symptoms	Afebrile, normal blood pressure, no orthostatic changes in blood pressure/pulse	May be afebrile or may develop fever with temperature >102.2°F (39.0°C); normal blood pressure; possible mild orthostatic blood pressure/pulse changes with or without mild orthostatic-related symptoms ^c ; sunken fontanelle ^d	Fever with temperature >102.2°F (39.0°C), low blood pressure, dizziness, severe abdominal pain

^a If signs of dehydration are absent, rehydration therapy is not required. Maintenance therapy and replacement of fluid losses in stool should be undertaken.

^b Signs and symptoms experienced, especially by young children.

^c Postural (orthostatic) hypotension is defined as a drop in the systolic and/or diastolic pressure of >15–20 mm Hg on movement from a supine to an upright position and may be associated with lightheadedness, dizziness, or fainting. On rising, the diastolic pressure normally remains the same or increases slightly, and the systolic pressure drops slightly. If the blood pressure drops, the pulse should be checked simultaneously; the pulse rate should increase as blood pressure drops. Failure of the pulse to rise points to a neurogenic problem (e.g., in diabetic patients with peripheral neuropathy) or may indicate that the patient is taking a beta blocker. The presence of orthostatic hypotension suggests that the patient has lost ≥ 1 L of vascular volume, and referral for medical care is necessary.

^a Signs and symptoms of concern in young infants. Source: Adapted from reference 20.

Children younger than 5 years and adults older than 65 years are at greater risk for complications than other age groups. In the United States, most children recover completely from diarrhea; however, approximately 1.7 per 100,000 young children die annually from complications of acute gastroenteritis.²³ Children 2 years of age and younger are more likely to suffer complications that necessitate hospitalization. In newborns, water may make up 75% of total body weight; severe diarrhea may cause water loss equal to 10% or more of body weight. After 8–10 bowel movements within a 24-hour period, a 2-month-old infant can potentially lose enough fluid to result in circulatory collapse and renal failure.

People 65 years of age and older are likely to experience more severe diarrhea than other adults and also may experience the highest rate of death from enteric infections.

Algorithm: Acute Diarrhea in Children 6 Months to 5 Years

Figure 16–1 Self-care for acute diarrhea in children 6 months to 5 years. Key: AIDS = Acquired immunodeficiency syndrome; BW = body weight; CVD = cardiovascular disease; D/C = discontinue; I.V. = intravenous; ORS = oral rehydration solution. (Source: Adapted from [references 24–26](#).)

Algorithm: Acute Diarrhea in Children Older than 5 Years

Figure 16–2 Self-care for acute diarrhea in children older than 5 years, adolescents, and adults. Key: D/C = Discontinue; ORS = oral rehydration solution.

Treatment of Diarrhea

Treatment Goals

The goals of self-treatment for diarrhea are to (1) prevent or correct fluid and electrolyte loss and acid–base disturbance, (2) control symptoms, (3) identify and treat the cause, and (4) prevent acute morbidity and mortality.

General Treatment Approach

Infectious diarrhea is often self-limiting. Initial self-management in both adults and children with mild to moderate, uncomplicated diarrhea should focus on fluid and electrolyte replacement by administering commercially available oral rehydration solutions (ORSs) in adequate doses ([Table 16–6](#)). Simultaneous implementation of oral rehydration and specific dietary measures is appropriate for treating mild to moderate diarrheal illness. Symptomatic control also can be achieved by using nonprescription antidiarrheal drugs, such as loperamide, in carefully selected patients. Patients with uncomplicated acute diarrhea who are otherwise healthy usually improve clinically within 24–48 hours; normal bowel function often is restored in 24–72 hours without additional treatment. If the condition remains the same or

worsens after 48 hours of onset, medical referral is necessary to prevent complications.^{24–26} Specific exclusions for self-treatment that require referral for medical evaluation are listed in [Figure 16–1](#).

Table 16–6 Composition of Selected Oral Rehydrating Solutions (ORSs) and Common Household Fluids

Solution/Fluid	Osmolarity (mOsm/L)	Sodium (mEq/L)	Potassium (mEq/L)	HCO₃[−] (mEq/L)	Carbohydrate (g/L)
WHO Recommendations					
Standard-osmolarity ORS	310	90	30	30	20
Reduced-osmolarity ORS	245	75	20	20	13.5
<i>Acceptable range</i>	200–310	60–90	15–25		
Commercially Available Products					
Ceralyte	235	70	20	10	40
Enfalyte	200	50	25	30	30
Pedialyte	250	45	20	30	25
Rehydralyte	310	75	20	30	25
Common Household Remedies					
Apple juice	700	3	20	0	100–150
Chicken broth	450	250	5	0	0
Colas	700	2	0.1	13	100–150
Gatorade	330	20	3	3	45
Ginger ale	565	3.5	0.1	3.6	90
Tea	5	0	0	0	0

Key: HCO₃[−] = Bicarbonate; WHO = World Health Organization.

With diarrhea of any severity in infants younger than 6 months of age, moderate diarrhea in children 2 years of age and younger, and unusually high fluid output, significant fever, or mental status changes in young children, evaluation by a primary care provider or a health care provider in an emergency department is always indicated (Figure 16–1).²² Severe diarrhea in any patient constitutes a medical emergency and necessitates immediate referral for medical evaluation and treatment with intravenous (IV) fluid therapy. Presence of blood or mucus in the stool also warrants medical evaluation. Certain medical conditions can increase the risk for dehydration. Referral for medical care should be considered for patients with diabetes, severe cardiovascular or renal diseases, concurrent respiratory tract infection, or multiple unstable chronic medical conditions. Patients with severe abdominal pain or cramping (particularly those older than 50 years of age) or abdominal tenderness or distention may have a complicating acute abdominal process, such as ischemic bowel disease, and should be referred for medical evaluation.²⁷ Immunocompromised patients, such as those receiving cancer treatment, organ transplant recipients, and patients with AIDS, also need medical evaluation, because their diarrheal illness often will be complicated and difficult to manage.

Self-care during pregnancy is not appropriate. Although diarrhea can be a normal physiologic occurrence during pregnancy, it may be a symptom of GI infection.²⁸ *C. jejuni* and *Salmonella* may cause severe, even fatal maternal infection. Furthermore, *C. jejuni*, *Salmonella*, and *Listeria* are recognized causes of intrauterine infection and perinatal death.^{28,29} Pregnant women experiencing diarrhea should consult a primary care provider or an obstetrician.

Nonpharmacologic Therapy

Fluid and Electrolyte Management

Rehydration using reduced osmolarity ORS is the preferred, first-line treatment for mild to moderate diarrhea. This approach is as effective as IV replacement therapy in managing fluid and electrolytes in children with mild to moderate dehydration secondary to diarrhea. Health care providers can safely recommend an ORS for mild to moderate diarrhea in patients with no exclusions to self-care.

Water absorption in the small intestine is passive and depends on the absorption of electrolytes and selected solutes such as sodium, chloride, glucose, small peptides, and amino acids. As these substances are absorbed, water accompanies their movement to maintain an isotonic state. Sodium ion transport is the primary mechanism controlling water movement. An active sodium–potassium adenosine triphosphatase pump present in enterocytes moves sodium into the cell in exchange for potassium ions. Other transport mechanisms include the sodium–glucose and sodium–amino acid cotransport processes (each of which transports these substances into the enterocytes) and the sodium luminal exchange mechanism. The sodium–glucose cotransport mechanism, in which glucose absorption is coupled with active transport of sodium, is important in the management of diarrhea. Unlike other sodium transport systems, the sodium–glucose cotransport mechanism is not adversely affected by most diarrheal diseases, and hypotonic ORSs containing low concentrations of glucose or dextrose (2%–2.5%) can be useful in managing fluid and electrolyte balance. The sugar molecules provide little caloric support but facilitate intestinal sodium and water absorption. Maximal sodium absorption occurs at a molar glucose-to-sodium ratio close to 1.

Depending on the patient's fluid and electrolyte status, oral treatment may be carried out in two phases: rehydration therapy and maintenance therapy. Rehydration over 3–4 hours quickly replaces water and electrolyte deficits to restore normal body composition. In the maintenance phase, electrolyte solutions are given to maintain normal body composition until adequate dietary intake is reestablished. [Figures 16–1](#) and [16–2](#) outline rehydration and maintenance therapies, including fluid and electrolyte recommendations for children and adults. Although use of an ORS generally is recommended for adults with diarrhea, little evidence supports this practice, and ORSs may not provide any real benefit to otherwise healthy adults with mild diarrhea who can maintain an adequate fluid intake. For these patients, fluid and electrolyte status can be maintained by increasing intake of fluids such as clear juices, soups, or sports drinks.

A variety of oral rehydration products are available ([Table 16–6](#)). Most products are premixed solutions; a few are available as dry powders of glucose and electrolytes that require the addition of water. The premixed products are preferred for use in children because they are safe and convenient; improper mixing of dry powders by caregivers has led to fluid and electrolyte complications and injury. All available premixed solutions are equally safe and

effective; there is no evidence that one product is clinically superior to another for rehydration. The World Health Organization (WHO) and United Nations Children's Fund (UNICEF) recommend use of an ORS containing 75 mEq/L of sodium.^{30,31} Compared with the previously recommended ORSs (which contained 90 mEq/L of sodium), this reduced-osmolality ORS significantly reduces the need for unscheduled IV therapy, the duration of diarrhea, stool output, and the incidence of vomiting in children with non-cholera diarrhea. This type of ORS also is effective in children and adults with cholera, although transient, asymptomatic hyponatremia may develop in adults. Rehydration solutions available in the United States contain 70–90 mEq/L of sodium; maintenance solutions contain 45–50 mEq/L of sodium.

Some cereal-based products use complex carbohydrates (e.g., rice syrup solids) instead of glucose. Complex carbohydrates are converted into glucose at the intestinal brush border and provide more cotransport molecules while reducing the osmotic load of the ORS. Cereal-based ORS therapy potentially reduces stool volume by 20%–30% in children with cholera but may not significantly alter stool volume in children with non-cholera acute diarrhea.

A variety of common household oral solutions also have been used for oral rehydration and maintenance ([Table 16–6](#)). These solutions may be sufficient to manage mild, self-limiting diarrhea in some patients, but they should be avoided if dehydration is a feature or in cases of moderate to severe diarrhea. Unlike commercial ORSs, these remedies are not formulated on the basis of the physiology of acute diarrhea. The content of these fluids is not equivalent to that of ORSs and may be inappropriate. The high carbohydrate content and osmolality of these solutions can worsen diarrhea, and their low sodium content can contribute to the development of hyponatremia. Sports drinks may be used in children older than 5 years and adults if additional sources of sodium, such as crackers or pretzels, are used concomitantly. Colas, ginger ale, apple juice, sports drinks, and similar products are not recommended for infants and young children (6 months to 5 years of age) with diarrhea. Tea, another popular household remedy, also is inappropriate for children because of its low sodium content. Chicken broth is not recommended because of its inappropriately high sodium content.

Dietary Management

Oral intake does not worsen diarrhea, and clinically significant nutrient

malabsorption is uncommon in acute diarrhea. In fact, during acute diarrhea, patients are able to absorb 80%–95% of dietary carbohydrates, 70% of fat, and 75% of the nitrogen from protein. Furthermore, early refeeding, in combination with maintenance oral rehydration, improves outcomes in children by reducing the duration of the diarrhea, decreasing stool output, and improving weight gain. If necessary, food should be withheld for no longer than 24 hours and be reintroduced using a normal, age-appropriate diet once the patient has been rehydrated, which should take no longer than 3–4 hours to accomplish.²² Most infants and children with acute diarrhea can tolerate full-strength breast milk and cow milk. The BRAT diet (bananas, rice, applesauce, and toast) is not recommended; it provides insufficient calories, protein, and fat, especially in situations of strict or prolonged use.²² Patients (or their parents or other caregivers) should be advised to avoid fatty foods; foods rich in simple sugars (e.g., carbonated soft drinks, juice, gelatin desserts), which can cause osmotic diarrhea; spicy foods, which may cause GI upset; and caffeine-containing beverages, which can promote fluid secretion and may worsen diarrhea.

There is no evidence that fasting or dietary modification influences outcomes of acute diarrhea in adults; however, the previous recommendations about foods to avoid can be applied if a normal diet is not tolerated.²²

Preventive Measures

Infectious diarrhea, especially acute viral gastroenteritis, often occurs in congregate living conditions such as daycare centers and nursing homes through person-to-person transmission. Isolation of the person affected with diarrhea, strict attention to handwashing, and use of sterile techniques are basic preventive measures that reduce the risk of transmission among such populations, including caregivers. Proper food handling, sanitation, and other hygienic practices help control transmission of bacteria and other infectious agents.

Although short-term bismuth subsalicylate (BSS) prophylaxis is frequently recommended to provide protection against travelers' diarrhea, the U.S. Food and Drug Administration (FDA) has deemed that available data are insufficient to support prophylactic use of BSS. However, the American College of Gastroenterology (ACG) has published a guideline on the use of BSS or loperamide to prevent and manage mild to moderate traveler's diarrhea.²⁴ Unless BSS is contraindicated (e.g., salicylate allergies; patients <12 years old

unless under medical supervision; children or teenagers recovering from influenza or varicella; current use of a salicylate product), the recommended dosing is 2.1 g 4 times daily (at meals and bedtime). This regimen may reduce risk by up to 60% and is most effective for trips lasting up to 2 weeks. Neither lower doses nor preventive use during trips lasting longer than 2 weeks has been shown to offer benefit. ACG recommends dosing of loperamide for a maximum of 48 hours and titration to maximum benefit while attempting to avoid drug-induced constipation. For patients with dysentery, use of loperamide, even when given concomitantly with antibiotics, may not be indicated in some cases of worsening symptoms.²⁴ Antibiotics with reliable activity against endemic enteropathogens (e.g., fluoroquinolones, rifaximin) provide effective prophylaxis. However, prophylactic antimicrobial agents are not currently recommended for most travelers.³² Prophylactic antibiotics may be considered for short-term travelers who are high-risk hosts (e.g., immunosuppressed patients) or travelers with underlying conditions that may be complicated by diarrheal illness, or for critical trips during which even a short bout of diarrhea could adversely affect the purpose of the trip.³²

Pharmacologic Therapy

Although in most cases acute, nonspecific diarrhea in the United States is self-limiting, nonprescription antidiarrheal products may provide symptom control and will usually do no harm when used according to label instructions. [Table 16–7](#) lists dosage and administration guidelines for these agents. However, evidence is lacking to show that pharmacologic agents other than loperamide and BSS reduce stool frequency or duration of disease in adults. [Table 16–8](#) lists available trade-name products that contain loperamide and BSS. No antidiarrheal drugs have been shown to significantly improve clinical outcomes for acute, nonspecific diarrhea in infants and children 5 years of age and younger.

Table 16–7 Recommended Dosages of Nonprescription Antidiarrheal Agents for Acute Diarrhea				
Medication	Dosage Forms	Adult Dosages (maximum daily dosage)	Pediatric Dosages	Duration of Use
Loperamide	Caplets (2 mg), liquid (1	Caplets: 4 mg initially, followed by 2 mg after each loose stool (not to exceed 8 mg/day)	Consult product instructions; not recommended	48 hours

Medication	Dosage Forms	Adult Dosages (maximum daily dosage)	Pediatric Dosages	Duration of Use
	mg/7.5 mL)	Liquid: 4 mg (30 mL) initially, followed by 2 mg (15 mL) after each loose stool (not to exceed 8 mg/day [60 mL/day])	for children <6 years except under medical supervision 6–8 years (48–59 lb [22–27 kg]): Caplets: 2 mg initially, followed by 1 mg after each loose stool (not to exceed 4 mg/day) Liquid: 2 mg (15 mL) initially, followed by 1 mg (7.5 mL) after each loose stool. Do not give >4 mg (30 mL) in 24 hours. 9–11 years (60–95 lb [27–43 kg]): Caplets: 2 mg initially, followed by 1 mg after each loose stool (not to exceed 6 mg/day) Liquid: 2 mg (15 mL) initially, followed by 1 mg (7.5 mL) after each loose stool. Do not give >6 mg (45 mL) in 24 hours.	
Bismuth subsalicylate	Tablets (262 mg), caplets (262 mg), liquids (262 mg/15 mL, 525 mg/	Tablets/caplets: 525 mg every 30–60 minutes up to 4200 mg/day (8 doses/day) Liquid: 262 mg/15 mL strength: 525 mg (30 mL) every 60 minutes up to 240 mL/day (8 doses/day); 525 mg/15 mL strength: 1050 mg (30 mL)	Not recommended for children <12 years except under medical supervision	48 hours

Medication	Dosage Forms	Adult Dosages (maximum daily dosage)	Pediatric Dosages	Duration of Use
	15 mL)	every 60 minutes up to 120 mL/day (4 doses/day)		
Digestive enzymes (lactase)	Chewable tablets, caplets, liquids	Tablets: 1-3 with first bite of dairy product Capsules: 1-2 with first bite of dairy products Liquid: 5-15 drops placed in or taken with dairy product	Same as adult dosage	Taken with each consumption of dairy product

Table 16–8 Selected Nonprescription Antidiarrheal Products

Trade Name	Primary Ingredient(s)
Loperamide Products	
Imodium A-D Caplets/Imodium EZ Chews (Tablets)	Loperamide HCl 2 mg
Imodium Advanced Caplets/Chewable Tablets	Loperamide HCl 2 mg; simethicone 125 mg
Imodium A-D Liquid	Loperamide HCl 1 mg/7.5 mL
Bismuth Subsalicylate Products	
Kaopectate Flavored Liquid (Cherry, Peppermint, Vanilla)	Bismuth subsalicylate 262 mg/15 mL (contains 130 mg of salicylate)
Kaopectate Extra Strength Peppermint Flavor Liquid	Bismuth subsalicylate 525 mg/15 mL (contains 236 mg of salicylate)
Kaopectate Antidiarrheal Caplets	Bismuth subsalicylate 262 mg (contains 99 mg of salicylate)
Maalox Total Relief Flavored Liquid (Peppermint, Strawberry)	Bismuth subsalicylate 525 mg/15 mL (contains 232 mg of salicylate)
Pepto-Bismol Caplets	Bismuth subsalicylate 262 mg (contains 99 mg of salicylate)
Pepto-Bismol Cherry Chewable Tablets	Bismuth subsalicylate 262 mg (contains 99 mg of salicylate)
Pepto-Bismol Chewable Tablets (Original,	Bismuth subsalicylate 262 mg (contains 102 mg of

Trade Name	Primary Ingredient(s)
InstaCool Peppermint)	salicylate)
Pepto-Bismol Liquid (Original, Cherry)	Bismuth subsalicylate 262 mg/15 mL (contains 130 mg of salicylate)
Pepto-Bismol Max Strength Liquid	Bismuth subsalicylate 525 mg/15 mL (contains 236 mg of salicylate)

Note: Pepto-Bismol adult formulations contain bismuth subsalicylate, but the products for children that contain calcium carbonate as the active ingredient are not listed.

Loperamide

The opioid agonist loperamide is a nonprescription antidiarrheal agent that provides symptomatic relief of acute, nonspecific diarrhea. When used according to the labeled instructions, loperamide is safe and effective. Loperamide reduces daily fecal volume, increases viscosity and bulk volume, and reduces fluid and electrolyte loss. It reduces peristalsis and increases intestinal transit time by stimulating peripheral micro-opioid receptors on the intestinal circular muscles to slow intestinal motility and allow absorption of electrolytes and water. Disruption of cholinergic and noncholinergic mechanisms involved in the regulation of peristalsis also may contribute to this effect. Loperamide also inhibits calcium channels and has antisecretory effects.

Loperamide undergoes extensive first-pass metabolism by cytochrome P450 (CYP) 3A4 and CYP2C8 to inactive metabolites and is a substrate for the efflux transporter P-glycoprotein (P-gP). These characteristics limit its bioavailability to 0.3%.^{33,34} P-gP also limits its distribution into the central nervous system (CNS), which minimizes risk for CNS adverse effects at the usual doses. When taken at very high doses or with inhibitors of CYP3A4, CYP2C8, or P-gP, loperamide can produce CNS effects and its plasma concentrations can reach toxic concentrations. At these concentrations, loperamide disrupts cardiac conduction to cause life-threatening and sometimes fatal cardiac dysrhythmias, including torsades de pointes.^{33–35}

Loperamide is increasingly being misused and abused to achieve euphoria or

to prevent opioid withdrawal symptoms, with such use often resulting in patient harm or death.^{36–38} In response, FDA requires a Boxed Warning about torsades de pointes and sudden death with use of higher-than-recommended doses in the prescription product labeling and limits the number of doses in a package of nonprescription-strength loperamide.³⁹

Loperamide may be used when the patient is afebrile or has a low-grade fever and does not have bloody stools. Nonprescription loperamide is labeled for use in children 6 years of age and older; the label for prescription loperamide provides directions for use in children as young as 2 years of age. However, use of loperamide in children younger than 6 years is not recommended because it produces only modest, clinically insignificant effects on stool volume and duration of illness but carries an unacceptably high risk for adverse effects, including life-threatening ileus and toxic megacolon.

Loperamide also is indicated for treatment of traveler's diarrhea (in combination with antibiotics) and chronic diarrhea associated with IBS and inflammatory bowel disease, as well as to reduce the volume of discharge from high-output ileostomies. Off-label uses include control of chronic diarrhea secondary to diabetic neuropathy and other conditions and control of toddler diarrhea (defined as diarrhea of at least 1 month's duration in an otherwise healthy, active, well-nourished child in whom stool examination has revealed no bacterial, viral, or protozoal pathogens). Off-label uses require medical supervision.

At usual doses ([Table 16–7](#)), loperamide has few adverse effects other than occasional dizziness and constipation. Infrequently occurring adverse effects include abdominal pain, abdominal distention, nausea, vomiting, dry mouth, fatigue, and hypersensitivity reactions. Loperamide generally is not recommended for use in patients with invasive bacterial diarrhea (due to enteroinvasive *E. coli*, *Salmonella*, *Shigella*, or *C. jejuni*) or antibiotic-associated diarrhea (due to *C. difficile*), because it may worsen the diarrhea or cause toxic megacolon or paralytic ileus. However, there is no evidence that these complications occur in actual practice when loperamide is used with appropriate antimicrobial therapy. Patients with signs or symptoms suggestive of infection with invasive organisms or antibiotic-associated diarrhea (i.e., positive fecal leukocyte smear, high fever, presence of blood or mucus in the stool) require medical evaluation for proper management. If abdominal distention, constipation, or ileus develops, loperamide should be discontinued.

Clinically significant drug–drug interactions are reported for loperamide ([Table 16–9](#)). Interactions with P-gP inhibitors (e.g., quinidine, ketoconazole, ritonavir) may result in a 2- to 3-fold increase in loperamide plasma concentrations. Concurrent administration of loperamide with other substrates for CYP3A4 and CYP2C8 (e.g., protease inhibitors, cyclosporine, erythromycin, clarithromycin) also may elevate loperamide plasma concentrations. These drug interactions do not appear to cause clinically significant CNS depression or toxicity when loperamide is used in the recommended doses; however, monitoring for loperamide-related adverse effects, especially when used with a P-gP inhibitor, is recommended.⁴⁰ Taking high doses of loperamide with P-gP inhibitors or CYP3A4 inhibitors may increase risk of cardiovascular events. Persons misusing or abusing loperamide have purposefully taken P-gP and CYP3A4 inhibitors with high doses of loperamide to enhance bioavailability and distribution of the drug into the CNS.³³ Loperamide may significantly decrease saquinavir concentrations, and patients taking saquinavir should be advised not to use loperamide, especially for long periods of time.

Bismuth Subsalicylate

BSS is FDA approved for management of acute diarrhea, including traveler’s diarrhea, in adults and children 12 years of age and older; it is not recommended for use in young children. BSS is also indicated for indigestion and as an adjuvant to antibiotics for treating *Helicobacter pylori*-associated peptic ulcer disease. The salicylate moiety exerts antisecretory antidiarrheal effects that reduce fluid and electrolyte losses, the frequency of unformed stools, nausea, and vomiting; increase stool consistency; and relieve abdominal cramping. Its antisecretory effects may be mediated by inhibition of prostaglandin synthesis, inhibition of intestinal secretion through stimulation of sodium and chloride reabsorption, or disruption of calcium-mediated processes that regulate intestinal ion transport. The bismuth moiety exerts direct antimicrobial effects against ETEC and EAEC, *C. jejuni*, and other diarrheal pathogens. These antimicrobial effects appear to be unimportant in the treatment of traveler’s diarrhea, although they may play a role in the benefits of prophylactic use of this drug. BSS also directly binds to enterotoxins produced by *E. coli* and other diarrheal pathogens; the clinical significance of this effect in the treatment of diarrhea is not clear.

[Table 16–7](#) provides dosing information for BSS. BSS is available in several dosage forms, with variable amounts of salicylate ([Table 16–8](#)). BSS should not

be used in patients taking aspirin or other salicylates because toxic salicylate levels may be reached, even when labeled dosing directions for each medication are followed.

Mild tinnitus, a dose-related adverse effect, may be associated with moderate to severe salicylate toxicity. If tinnitus occurs, the product should be discontinued and the patient referred for medical evaluation. Salicylates may cause adverse effects that are independent of the dose. In susceptible patients, salicylate-induced gout attacks have occurred. Patients who are sensitive to aspirin (i.e., experience asthmatic bronchospasm) should not use BSS.

Because of the risk of Reye syndrome, a rare but serious illness, children and adolescents who have or are recovering from chickenpox or influenza-like illness should not use BSS.⁴¹ BSS also should not be taken within 6 weeks of receiving the chickenpox or influenza vaccine, as these vaccines may enhance the adverse effect of salicylates. With use of BSS in pediatric patients, changes in behavior with nausea and vomiting should prompt referral for medical evaluation, as these disturbances may be early signs of Reye syndrome. Children's Pepto Antacid contains calcium carbonate as the active ingredient and, unlike other forms of Pepto-Bismol, is not associated with Reye syndrome; however, it is not labeled for treatment of diarrhea. (See [Chapter 5](#) for further information.)

BSS has rarely been associated with neurotoxicity. Encephalopathy characterized by slow onset of tremors, postural instability, ataxia, myoclonus, poor concentration, confusion, memory impairment, seizures, visual and auditory hallucinations, psychosis, delirium, and depression, potentially eventuating in death, can occur when bismuth concentrations in the blood exceed 50 mcg/L. Use of BSS in the recommended doses, even for several weeks, such as in prophylaxis for traveler's diarrhea, produces mean blood concentrations well below 50 mcg/L and does not result in bismuth-related neurotoxicity. However, patients with AIDS who are experiencing acute diarrhea may be at particular risk for bismuth encephalopathy, perhaps resulting from altered GI absorption, and should not use BSS.

Harmless black staining of stool (which should not be confused with melena) and darkening of the tongue are seen in more than 10% of patients treated with BSS. Bismuth salts react with hydrogen sulfide produced by bacteria in the mouth and colon to produce the discoloration. Stains may be removed by

brushing the tongue with a soft-bristled brush, or the discoloration will cease on discontinuation of the BSS.

Bismuth is radiopaque and may interfere with radiographic intestinal studies. BSS may interact adversely with a number of other drugs, particularly those that potentially interact with aspirin (Table 16–9). The salicylate moiety can increase the risk of toxicity with warfarin, valproic acid, and methotrexate by significantly decreasing plasma protein binding of these drugs in vivo. Salicylate also can increase the plasma concentration of methotrexate by decreasing its renal clearance. The uricosuric effects of probenecid may be inhibited by the salicylate moiety. The bismuth moiety is a trivalent cation and may decrease absorption of other medications, such as tetracycline and quinolone antibiotics, by forming complexes with them in the GI tract. Solid dosage forms of BSS contain calcium carbonate, which may enhance this interaction. When fluoroquinolones are used to treat traveler’s diarrhea, the patient should be instructed to discontinue BSS.

Table 16–9 Clinically Important Drug–Drug Interactions With Nonprescription Antidiarrheal Agents

Antidiarrheal	Drug/Herbal Product	Potential Interaction	Management/Preventive Measures
Bismuth subsalicylate	Carbonic anhydrase inhibitors (e.g., acetazolamide, methazolamide) ^a	Increased risk for severe metabolic acidosis and/or salicylate toxicity	Avoid high-dose salicylate therapy; if concurrent administration is necessary, monitor closely for toxicity.
	Insulin ^b	Increased risk of hypoglycemia	Monitor glucose levels more frequently and adjust insulin dose, if necessary.
	Methotrexate	Increased risk of methotrexate toxicity	Avoid salicylate therapy within 10 days of high-dose methotrexate; if concurrent administration is necessary, monitor closely for toxicity.
	Pramlintide	Increased risk of hypoglycemia	Give bismuth subsalicylate 1 hour before or 2 hours after pramlintide; monitor glucose levels more frequently and adjust insulin dose, if necessary.

Antidiarrheal	Drug/Herbal Product	Potential Interaction	Management/Preventive Measures
	Probenecid	Increased risk of hyperuricemia	Avoid persistent high-dose salicylate therapy; occasional small doses are not clinically significant.
	Sulfinpyrazone	Increased risk of hyperuricemia	Avoid persistent high-dose salicylate therapy; occasional small doses are not clinically significant.
	Tetracyclines (systemic)	Decreased tetracycline effectiveness	Avoid concurrent use; if such use cannot be avoided, tetracycline should be taken at least 2–3 hours before bismuth subsalicylate dose. Monitor for antibiotic efficacy.
	Warfarin	Increased risk of bleeding	Avoid concurrent use, if possible. Monitor international normalized ratio (INR) closely whenever bismuth subsalicylate is added or discontinued, and adjust warfarin dose as necessary.
Loperamide	Eliglustat	Increased loperamide concentrations with enhanced central effects	Avoid concurrent use. If such use cannot be avoided, monitor for loperamide-related CNS adverse effects.
	Lomitapide	Increased loperamide concentrations with enhanced central effects	Avoid concurrent use. If such use cannot be avoided, monitor for loperamide-related CNS adverse effects.
	Nilotinib	Increased loperamide concentrations with enhanced central effects	Avoid concurrent use. If such use cannot be avoided, monitor for loperamide-related CNS adverse effects; consider ECG monitoring for patients at high risk for QT interval prolongation.
	Saquinavir	Decreased saquinavir plasma concentrations and increased loperamide plasma	Avoid concurrent use. If such use cannot be avoided, consider ECG monitoring for patients at high risk for QT interval prolongation.

Antidiarrheal	Drug/Herbal Product	Potential Interaction	Management/Preventive Measures
		concentrations.	
	Simeprevir	Increased loperamide concentrations with enhanced central effects	Avoid concurrent use. If such use cannot be avoided, monitor for loperamide-related CNS adverse effects.
	St. John's wort	Increased risk of delirium with confusion, agitation, and disorientation	Monitor for signs of altered mental status.
	Valerian	Increased risk of delirium with confusion, agitation, and disorientation	Monitor for signs of altered mental status.

^a Although this interaction has not been reported with ocular carbonic anhydrase inhibitors, the possibility should be considered.

^b Including insulin, insulin lispro, insulin aspart, recombinant, insulin glulisine, insulin detemir, and insulin degludec.

Key: CNS = Central nervous system; ECG = electrocardiogram.

Source: Adapted from Vandenbossche J, Huisman M, Xu Y, et al. Loperamide and P-glycoprotein inhibition: assessment of the clinical relevance. *J Pharm Pharmacol*. 2010;62(4):401–12; Micromedex[®] (electronic version). IBM Watson Health, Greenwood Village, CO. Available at: <https://www-micromedexsolutions-com.proxy.lib.umich.edu/>; Lexicomp Online. Wolters Kluwer Clinical Drug Information, Inc. 2016.

Digestive Enzymes

For patients with lactase deficiency who are intolerant of milk products, lactase enzyme preparations (**Table 16–10**) may be taken with milk or other dairy products to prevent osmotic diarrhea.

Table 16–10 Selected Lactase Enzyme Products

Trade Name	Primary Ingredient
Lactaid Original Caplets	Lactase enzyme 3000 FCC units ^a /caplet
Lactaid Fast Act Caplets	Lactase enzyme 9000 FCC units ^a /caplet
Lactaid Fast Act Chewable Tablets	Lactase enzyme 9000 FCC units ^a /tablet
Lacteeze Children's	Lactase enzyme 3000 FCCLU/tablet
Lacteeze Drops	Lactase enzyme 80 FCCLU/5 drops
Lacteeze Extra Strength Tablets	Lactase enzyme 4000 FCCLU/tablet
Lacteeze Ultra Caplets	Lactase enzyme 9000 FCCLU/tablet
Lactrase Capsules	Lactase enzyme 250 mg/capsule

^a FCC units are standardized units established by the Food Chemicals Codex, a compendium of internationally recognized standards for purity and identity of food ingredients published by the United States Pharmacopeia.

Key: FCC = Food Chemicals Codex; FCCLU = FCC lactase units.

Product Selection Guidelines

Table 16–7 provides a quick reference for the recommended dosage and duration of therapy for selected antidiarrheal agents. **Tables 16–8** and **16–10** list dosage forms and primary ingredients of selected trade-name products.

In May 2011, FDA released final guidance on nonprescription liquid products that include any type of measuring device, such as the dropper packaged with lactase drops.⁴² Other devices mentioned include cups, syringes, and spoons. The key points of the guidance are the following recommendations:

- A dosing device should be included with all oral liquid nonprescription products.
- The device should be calibrated to the dose recommended in the product directions.
- The device should be used only with the product in which it is

- packaged.
- The markings should remain visible even when the liquid is in the device.

Special Populations

For young children (up to 5 years of age), self-care measures are limited to treating dehydration with ORS; antidiarrheal medications are not recommended. BSS-containing products should not be used in children and adolescents, especially those recovering from chickenpox or influenza, because of the risk of Reye syndrome. (See [Chapter 5](#) for further information.)

If diarrhea persists despite ORS therapy, a primary care provider must be consulted.

Older patients (65 years of age and older) should be strongly cautioned against self-treatment with antidiarrheal medications. Diarrhea in these patients is more likely to be severe or possibly fatal; therefore, patients in this age group should be referred for medical evaluation.

Use of nonprescription antidiarrheals may be inappropriate during pregnancy; therefore, pregnant women also should be referred for medical evaluation before self-treating, especially if signs and symptoms of persistent diarrhea, weight loss, malnutrition, or fever or manifestations of volume depletion are present.^{43–45} (See the Preface for a detailed explanation of the pregnancy data.)

BSS-containing products are contraindicated during pregnancy because of concerns that the salicylate component may inhibit platelet function and, in the third trimester, cause premature closure of the fetal ductus arteriosus. Nursing women generally should avoid BSS.

Patient Factors and Preferences

Selection of antidiarrheal products for older children and adults should be based on factors such as the etiology of the diarrhea (if known), prominent signs and symptoms, potential interactions with prescribed medications, and applicable contraindications. For example, BSS is suggested to be the preferred agent when vomiting is the predominant clinical sign of acute gastroenteritis. BSS should not be used to treat diarrhea in

immunocompromised patients (e.g., those with AIDS, transplant recipients), because they are at increased risk for bismuth encephalopathy. Patient preference for a particular dosage form and products requiring fewer doses also should be considered.

Complementary Therapies

Probiotics may be used to reduce the severity and duration of symptoms in immunocompetent adults and childrens.³⁰ Convincing evidence suggests that probiotics, including several *Lactobacillus* species, *Bifidobacterium lactis*, and *Saccharomyces boulardii*, are effective in preventing and treating mild acute, uncomplicated diarrhea, in previously healthy infants and children, especially rotavirus diarrhea and antibiotic-associated diarrhea.^{46,47} (See [Chapter 20](#) for a discussion of probiotics.) Probiotics support gut health by several mechanisms: They release antimicrobial substances in the intestines, produce acids (e.g., lactic acid) and short-chain fatty acids that lower intestinal pH and suppress growth of pathogenic bacteria, enhance mucosal barrier integrity and immune responses, and compete with pathogenic bacteria for intestinal mucosal binding sites. However, a role for these products in the management of moderate to severe diarrhea is not supported conclusively by available evidence.⁴⁸

Probiotics appear to be safe for most patients. Major adverse effects, such as *Lactobacillus* or *Saccharomyces* sepsis, rarely occur. Older, critically ill, and immunocompromised patients and patients with severe bowel diseases are at risk for systemic infection from probiotic use. The American Academy of Pediatrics has a conservative recommendation for the use of probiotics to be considered in special circumstances, such as for children in long-term health care facilities or care centers.⁴⁹ Probiotics are recognized by FDA as dietary supplements or components of functional foods, which limits the health claims that can be made for them, and they should not be recommended for self-treatment for or prevention of acute, uncomplicated diarrhea.

Compelling evidence demonstrates that daily zinc supplementation reduces the duration, severity, and persistence of acute diarrhea in children younger than 5 years of age, especially in countries with a high incidence of zinc deficiencies. Since 2004, WHO and UNICEF have recommended routine zinc supplementation for 10–14 days in children with acute diarrhea, in addition to ORS.³⁶ Zinc produces antidiarrheal effects by stimulating intestinal water and

electrolyte absorption, preventing villous atrophy, and enhancing overall immunity, perhaps in part through upregulation of T-helper cell (Th1 cell) immune responses, including macrophage activation and cell-mediated immunity. Zinc supplementation may be of no benefit in developed countries, where zinc deficiency is rare; therefore, its use is not routinely recommended.²⁹ Of note, zinc supplementation is associated with an increased risk for vomiting.

There is no evidence to substantiate the safety and effectiveness of herbal products and homeopathic remedies in the management of acute diarrheal diseases. Therefore, their use cannot be recommended.

Assessment of Diarrhea: A Case-Based Approach

To evaluate patients with diarrhea, the health care provider identifies relevant signs and symptoms and then makes clinical judgments. This assessment is based on the patient's responses to questions designed to help determine the cause of the specific signs and symptoms, their characteristics, and their severity (**Tables 16–1** and **16–4**). Important information to ascertain includes onset, duration, severity, degree of dehydration, vital signs (to determine the presence of fever), recently ingested foods or recent international travel destinations, current medications, and other symptoms to determine the patient's susceptibility to complications. Persistent or chronic diarrhea precludes self-treatment and necessitates immediate medical referral, as does the presence of high fever (temperature $>102.2^{\circ}\text{F}$ [39.0°C]), protracted vomiting, abdominal pain in patients older than 50 years, or blood or mucus in the stool. In the absence of any of these significant findings, the degree of dehydration should then be assessed (**Table 16–4**); the provider should ask about the nature and amount of fluid intake. Severity of dehydration can be accurately assessed by evaluating changes in body weight. For example, in children, mild dehydration is associated with a 3%–5% loss of body weight, whereas severe dehydration is associated with a loss of more than 9%. However, the patient (or the parent or caregiver) seldom knows the exact weight before the onset of diarrhea for comparison, and distinguishing between mild and moderate dehydration may be difficult.

The initial assessment of a pediatric patient also should seek to determine plausible causes of signs and symptoms. The common clinical manifestations of acute gastroenteritis (e.g., vomiting, loose stools, fever) are nonspecific findings associated with many other childhood diseases (e.g., acute otitis media, bacterial sepsis, meningitis, pneumonia, urinary tract infections). This determination is a key factor in recommending a proper course of action, which may include self-treatment or referral for medical evaluation. A complete medication history must be obtained before a product is selected.

Physical assessment of a patient with symptoms of diarrhea can provide information useful in assessing the severity of the diarrhea ([Table 16–4](#)). Checking skin turgor and moistness of oral mucous membranes will help determine the degree of dehydration. Vital signs (e.g., pulse, temperature, respiration, blood pressure) are important indicators of illness severity and should be routinely measured. Symptoms of moderate to severe dehydration may include postural (orthostatic) hypotension, defined as a drop in the systolic and/or diastolic pressure of greater than 15–20 mm Hg when a patient moves from a supine to an upright position. Normally, the diastolic pressure remains the same or increases slightly and the systolic pressure drops slightly on rising. If the blood pressure drops, the pulse should be checked simultaneously; the pulse rate should increase as blood pressure drops. Failure of the pulse to rise suggests that the problem is neurogenic (e.g., in diabetic patients with peripheral neuropathy) or that the patient may be taking a beta blocker. The presence of orthostatic hypotension suggests that the patient has lost 1 L or more of vascular volume, and referral for medical care is necessary.

Cases 16–1 and 16–2 provide examples of assessment of two different patients with diarrhea.

Case 16–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms	

Relevant Evaluation Criteria	Scenario/Model Outcome
and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient describes intermittent diarrhea occurring for the past 3 years. She also reports abdominal cramping with watery bowel movements with a large amount of flatulence several times per week. Denies vomiting, fever, blood in stool, weight loss, or other relevant signs or symptoms. Has not traveled internationally recently.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Ingestion of milk products
c. Description of the patient's efforts to relieve the symptoms	None. She acknowledges: "I thought it would get better by itself, but it hasn't."
d. Patient's identity	Alice Kim
e. Patient's age, gender, height, and weight	27 years, female, 5 ft 6 in., 150 lb (68.04 kg)
f. Patient's occupation	Teacher
g. Patient's dietary habits	She eats a well-balanced diet, although she likes dessert (especially ice cream); drinks wine and beer several times weekly.
h. Patient's sleep habits	Sleeps 8 hours per night.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	None
j. Allergies	NKA
k. History of other adverse reactions to medications	None
l. Other (describe) _____	n/a
Assess	

Relevant Evaluation Criteria	Scenario/Model Outcome
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s) (Table 16-1).	Patient appears to have food-induced diarrhea, likely as a consequence of lactose intolerance.
3. Identify exclusions for self-treatment (Figure 16-1).	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer Ms. Kim to an appropriate health care provider. (2) Recommend self-care with a nonprescription lactase enzyme product and nondrug measures, such as keeping a food log and dietary modifications. (3) Recommend self-care with a nonprescription lactase enzyme product and nondrug measures, such as keeping food log and dietary modifications, until the patient can see an appropriate health care provider. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Ms. Kim has no exclusions for self-care. It is appropriate to recommend self-care with a nonprescription product.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Lactase enzyme products are the preferred treatment for symptomatic relief of your diarrhea. You may continue your regular diet during treatment, but you should avoid the consumption of foods high in lactose (such as milk or ice cream)."
7. Explain to the patient or caregiver the rationale for selecting the recommended	"Nonprescription antidiarrheal products are safe and effective in managing symptoms of food-induced diarrhea when no fever or signs of serious infection are present."

Relevant Evaluation Criteria	Scenario/Model Outcome
therapeutic approach from the considered therapeutic alternatives.	
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
a. Appropriate dose and frequency of administration	See the box “Patient Education for Diarrhea.”
b. Maximum number of days the therapy should be employed	See the box “Patient Education for Diarrhea.”
c. Product administration procedures	See the box “Patient Education for Diarrhea.”
d. Expected time to onset of relief	See the box “Patient Education for Diarrhea.”
e. Degree of relief that can be reasonably expected	See the box “Patient Education for Diarrhea.”
f. Most common adverse effects	See the box “Patient Education for Diarrhea.”
g. Adverse effects that warrant medical intervention should they occur	See the box “Patient Education for Diarrhea.”
h. Patient options in the event that condition worsens or persists	See the box “Patient Education for Diarrhea.”
i. Product storage requirements	Store in a cool, dry place out of children’s reach.
j. Specific nondrug measures	See the box “Patient Education for Diarrhea.”

Relevant Evaluation Criteria	Scenario/Model Outcome
Solicit follow-up questions from the patient or caregiver.	"What kind of changes to my diet should I make?"
Answer the patient's or caregiver's questions.	"Avoid or minimize foods high in lactose content. If you are not sure, you should check food labels to note if a product contains lactose, milk products, dry milk solids, or whey. You can take the lactase enzymes with the first bite or drink of a dairy product to prevent symptoms. You may also continue to take another dose after 30–45 minutes if you continue to eat that product."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Ms. Kim in 1–2 days to evaluate her response to your recommendations.

Key: n/a = Not applicable; NKA = no known allergies.

Case 16–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	A patient comes to the pharmacy for a recommendation. She complains of diarrhea starting the previous night and reports an average of 3 loose stools since. She went to a local Italian restaurant yesterday for lunch, where she had Alfredo pasta with chicken. She feels nauseous but has not vomited.
b. Description of any factors	None noted

Relevant Evaluation Criteria	Scenario/Model Outcome
that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	
c. Description of the patient's efforts to relieve the symptoms	"I borrowed some of my friend's Lactaid this morning, but it didn't work."
d. Patient's identity	Laura Richards
e. Patient's age, gender, height, and weight	25 years, female, 5 ft 2 in., 175 lb (78.18 kg)
f. Patient's occupation	Waitress
g. Patient's dietary habits	Reports a well-balanced diet that is mostly plant-based. Eats 3 meals a day. Drinks alcohol occasionally in social situations. Drinks 1 cup of coffee every morning.
h. Patient's sleep habits	Sleeps 6–7 hours nightly.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	<i>Medical conditions:</i> none
	<i>Medications:</i> An OTC women's daily vitamin
j. Allergies	Penicillin (rash)
k. History of other adverse reactions to medications	None
l. Other (describe) _____	n/a
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s) (Table 16-1).	Patient appears to have acute diarrhea, most likely of viral etiology.
3. Identify exclusions for self-treatment (Figure 16-1).	None

Relevant Evaluation Criteria	Scenario/Model Outcome
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer Mrs. Richards to an appropriate health care provider. (2) Recommend self-care with a nonprescription antidiarrheal product, such as loperamide, and nondrug measures, such as maintaining hydration with an ORS. (3) Recommend self-care with a nonprescription antidiarrheal product, such as loperamide, and nondrug measures, such as taking an ORS, until patient can see an appropriate health care provider. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Patient has mild to moderate diarrhea and no exclusions for self-care. It is appropriate to recommend self-care with a nonprescription antidiarrheal product. The patient needs appropriate education on the use of Lactaid.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Loperamide is the preferred treatment for symptomatic relief of your diarrhea. You should take 4 mg (2 tablets) now, and then 2 mg (1 tablet) with each subsequent loose stool. Do not take more than 8 mg (4 tablets) per day. You may continue your regular diet during treatment, but you should increase your intake of fluids to prevent dehydration."
	"Lactaid is not an antidiarrheal agent and will likely not help with your current symptoms. Lactaid is used for people with intolerance to dairy products and is meant to be taken with the first bite of food containing dairy, to help prevent symptoms such as gas and bloating in those with intolerance to dairy."
7. Explain to the patient or caregiver the rationale for selecting the recommended	"Nonprescription antidiarrheal products are safe and effective in managing symptoms of acute diarrhea when no fever or signs of serious infection are present. If no

Relevant Evaluation Criteria	Scenario/Model Outcome
therapeutic approach from the considered therapeutic alternatives.	improvement occurs within 2 days, or if symptoms worsen with nonprescription therapies, you may need to see an appropriate health care provider for further evaluation and treatment of your symptoms.”
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
a. Appropriate dose and frequency of administration	“You should take 4 mg (2 tablets) now, and then 2 mg (1 tablet) with each subsequent loose stool. Do not take more than 8 mg (4 tablets) per day. You may continue your regular diet during treatment, but you should increase your intake of fluids to prevent dehydration.”
b. Maximum number of days the therapy should be employed	8 mg/24 hours. Maximum duration of use is 48 hours.
c. Product administration procedures	Administer by oral route.
d. Expected time to onset of relief	Time to onset of effect is 1–3 hours.
e. Degree of relief that can be reasonably expected	No unformed stools within 48–72 hours of starting loperamide
f. Most common adverse effects	Loperamide generally is well tolerated. Adverse effects may include dizziness, constipation, nausea, or abdominal cramping, dry mouth, or fatigue.
g. Adverse effects that warrant medical intervention should they occur	Hypersensitivity reactions, severe abdominal pain, abdominal distention, severe or frequent nausea/vomiting
h. Patient options in the event that condition worsens or persists	“See an appropriate health care provider for further evaluation and treatment. Stay well hydrated in the meantime with an ORS until you can be seen.”

Relevant Evaluation Criteria	Scenario/Model Outcome
i. Product storage requirements	Store in a cool, dry place out of children's reach.
j. Specific nondrug measures	Rehydration using an ORS is the preferred nonpharmacologic treatment for symptoms of mild to moderate diarrhea.
Solicit follow-up questions from the patient or caregiver.	"Would it help if I changed my diet until this resolves?"
Answer the patient or caregiver's questions.	"Changes to your diet usually are not needed nor are they recommended in mild to moderate diarrheal disease. You may want to avoid fatty foods or foods that aggravate your symptoms, but I would encourage you continue to eat a normal, healthy diet, because it provides adequate nutrition to help your intestines to heal."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Mrs. Richards in 1-2 days to evaluate her response to your recommendations.

Key: n/a = Not applicable; ORS = oral rehydration solution; OTC = over-the-counter.

Patient Counseling for Diarrhea

Patients with diarrhea may focus on the need for a nonprescription medication to stop the frequent bowel movements. The health care provider should emphasize that most episodes of acute diarrhea stop after 48 hours and that preventing dehydration is the most important component of treatment. Counseling on the two-step treatment of dehydration and the need for dietary management should follow. For infants and children, educating parents and caregivers on the appropriate use of an ORS (including appropriate volumes to administer, rates of administration, and use in vomiting) and of dietary management is very important. For patient safety reasons, premixed solutions are preferred. If dry powder ORS is selected, however, the provider should give parents or other caregivers explicit

directions for mixing and verify that they understand the directions. For families with infants, CDC recommends maintaining a household supply of an ORS, because its early administration at home is vital if hospitalization is to be avoided. If travelers are using ORS dry powder in developing countries, only potable water should be used to reconstitute the powder.

If an antidiarrheal product is recommended:

Review label instructions with the patient or caregiver.

Calculate an appropriate dosage on the basis of the patient's age and weight, and emphasize the maximum number of doses that can be taken in 24 hours.

Explain potential drug interactions, adverse effects, contraindications, and the maximum duration of treatment before the patient should seek medical help.

The box "Patient Education for Diarrhea" contains specific information to provide in patient counseling.

Evaluation of Patient Outcomes for Diarrhea

Many patients have mild to moderate diarrhea that generally is self-limiting within 48 hours. Mild to moderate diarrhea is managed with ORSs, symptomatic drug therapy, and dietary measures. The patient should be monitored for dehydration by measuring body weight, vital signs, and mental alertness. With effective symptomatic treatment, the patient can expect reduced stool frequency and return to normal consistency of stools, as well as a reduction in generalized symptoms such as lethargy and abdominal discomfort. As the diarrhea resolves, the patient's appetite will return to normal and the patient can resume a regular diet.

Medical referral is necessary if any of the following signs and symptoms occur before or during treatment: high fever, worsening illness, bloody or mucoid stools, persistence of diarrhea beyond 48 hours, or signs of worsening dehydration (e.g., low blood pressure, rapid pulse, mental confusion). Also, medical referral is advised for infants, young children, frail patients of advanced age, pregnant patients, and patients with chronic illness (e.g., diabetes) at risk for secondary complications.

Patient Education for Diarrhea

The primary objective of self-treatment is to prevent excessive fluid and electrolyte losses. For most patients, carefully following product instructions and the self-care measures listed here will help ensure optimal outcomes.

Nondrug Measures

Infants and Children 6Months to 5Years of Age

- For mild to moderate diarrhea, indicated by passage of 3–5 unformed bowel movements per day, give the child or infant an oral rehydration solution (ORS) at a volume of 50–100 mL/kg of body weight over 2–4 hours to replace the fluid deficit. Give additional ORS to replace ongoing losses. Continue to give the solution for the next 4–6 hours or until the child is rehydrated.
- If the child is vomiting, give 1 teaspoon of the ORS every few minutes.
- If the child is not dehydrated, give 10 mL/kg or ½–1 cup of the ORS for each bowel movement, or 2 mL/kg for each episode of vomiting. As an alternative, to replace ongoing fluid losses, children weighing less than 22 lb (10 kg) should be given ¼–½ cup (60–120 mL) of ORS for each vomiting or diarrheal episode, and children weighing more than 22 lb (10 kg) should be given ½–1 cup (120–240 mL) for each vomiting or diarrheal episode.
- After the child is rehydrated, reintroduce food appropriate for the child's age, while also administering an ORS for maintenance therapy.
- If breastfeeding an infant with diarrhea, continue the breastfeeding. If the infant is bottle-fed, consult your primary care provider or pediatrician about replacing a milk-based formula with a lactose-free formula.
- Give children complex carbohydrate-rich foods, yogurt, lean meats, fruits, and vegetables. Do not give them fatty foods or sugary foods. Sugary foods can cause osmotic diarrhea.

- Do not withhold food for more than 24 hours.

Adults and Children Older Than 5 Years of Age

- For mild to moderate dehydration, indicated by a 3%–9% drop in body weight or passage of 3–5 unformed stools per day, drink 2–4 L of an ORS over 4 hours.
- If not dehydrated, drink $\frac{1}{2}$ –1 cup (120–240 mL) of an ORS or household fluids after each unformed bowel movement.
- If no medical conditions exist, sports drinks (with salty crackers or similar sodium source), diluted juices, soups, and broths may be consumed until the diarrhea stops.
- Do not withhold food for more than 24 hours.

Nonprescription Medications

- See [Table 16–6](#) for dosages of loperamide and bismuth subsalicylate.

Loperamide

- Note that loperamide can cause dizziness and constipation.
- Nonprescription loperamide is not recommended for children younger than 6 years, except under the supervision of a primary care provider or pediatrician.
- If loperamide is not effective in treating your diarrhea (if no clinical improvement is observed in 48 hours), check with your primary care provider or pharmacist about using a different nonprescription medication. You may have a bacterial diarrhea or pseudomembranous colitis; these conditions require specific antibiotic therapy that loperamide cannot treat.

Bismuth Subsalicylate

- Note that bismuth subsalicylate can cause a dark discoloration of the tongue and stool.
- Do not take this medication if you also are taking tetracyclines or other medicines for gout (uricosurics).

- Do not give this medication to children younger than 12 years.
- Do not give this medication to children or teenagers who have or are recovering from chickenpox or influenza-like symptoms, because of the risk of Reye syndrome.
- Do not give this medication to patients with AIDS.
- Do not take this medication if you are sensitive to aspirin, have a history of gastrointestinal bleeding, or have had problems with blood coagulation.

When to Seek Medical Attention

- If the diarrhea has not resolved after 72 hours of initial treatment, see your primary care provider.
- Monitor for excessive number of bowel movements, signs of dehydration, high fever, or blood in the stool. If any of these complications are present, discontinue bismuth subsalicylate, and consult your primary care provider.

Key Points for Diarrhea

- Self-treatment of diarrhea should be limited to patients with mild to moderate acute diarrhea who have minimal, mild, or moderate dehydration. Patients who appear volume-depleted, weak, dizzy, febrile (temperature $>102.2^{\circ}\text{F}$ [39.0°C]), or hypotensive should be referred for evaluation.
- ORS is the mainstay of therapy and should be used to rehydrate patients with minimal or mild to moderate dehydration.
- Rehydration should be performed rapidly (i.e., within 3–4 hours). Additional ORS should be given to maintain hydration and replace ongoing fluid losses resulting from diarrheal stools and/or vomiting (Figures 16–1 and 16–2).
- Patients or their caregivers should be instructed how to prepare

and administer an ORS.

- An age-appropriate, unrestricted diet should be initiated as soon as the patient is rehydrated. Food should be withheld for no more than 24 hours.
- Loperamide and BSS may be used to help control acute diarrhea in carefully selected patients.
- Antibiotic therapy generally is not indicated for patients with acute diarrhea unless it is traveler's diarrhea.

Chapter 17: Anorectal Disorders

Authors: Juliana Chan

Anorectal disorders are common and may be observed in any patient population. Most often, anorectal complaints involve the perianal canal, anal canal, and/or lower rectum. The most common conditions affecting the anorectal area include hemorrhoids; anal fistula, fissure, or abscess; and pruritus ani.^{1,2} Because these disorders affect the anus, patients often feel embarrassment in seeking medical attention. It is therefore imperative for the health care provider to be confident and discreet in conveying reassurance that anorectal symptoms are commonplace and warrant appropriate assessment and treatment as with any other health problem.

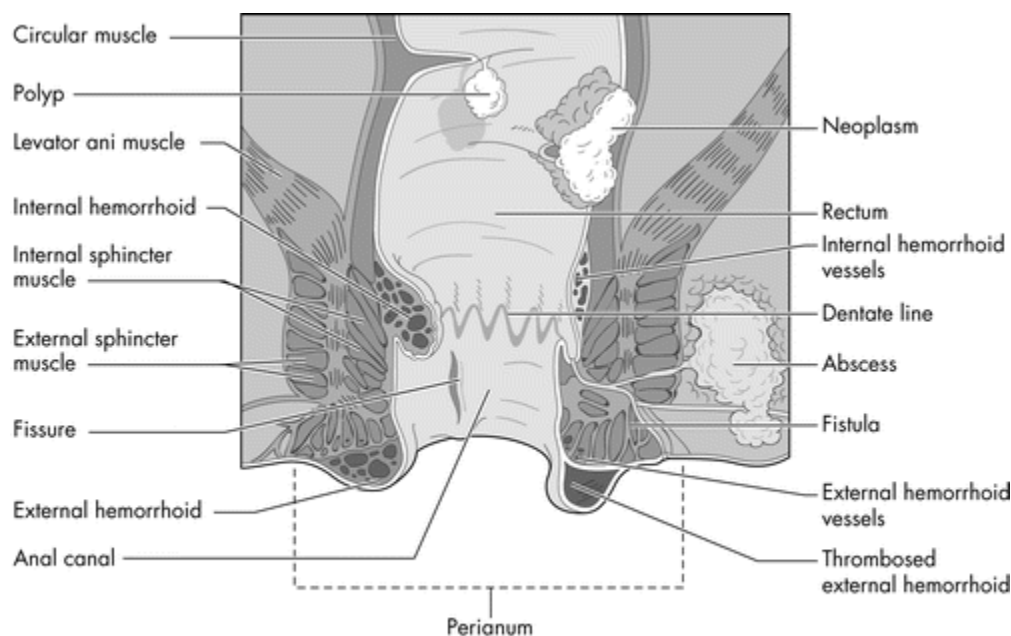
Of all the anorectal disorders, hemorrhoids constitute the most common complaint for which patients seek medical attention in the outpatient setting.^{1,3,4} Men and women, especially those older than 45 years of age, are equally likely to experience hemorrhoidal symptoms.^{4,6} Although epidemiologic data may vary and the true prevalence may be underreported in the United States, approximately 4.4% of the general population have hemorrhoids.^{2,4,6} In a cross-sectional study evaluating the employer-insured population, an estimated 1.4 million ambulatory care visits in 2014 were due to hemorrhoids, equating to an annual cost of more than \$700 million.⁴ This cost may be underestimated, however, because the relevant study was retrospective in design, and not all payer groups were evaluated; with proper extrapolation of the data, the financial burden may amount to more than \$1.6 billion.⁴ In 2004 the National Institutes of Health reported that approximately 2 million prescriptions were obtained to treat hemorrhoids.^{4,7} In 2014, an estimated \$88 million was devoted to hemorrhoid prescriptions; of interest from a global perspective, in 2017, \$136 million was spent worldwide on Preparation H.⁴

Pathophysiology of Anorectal Disorders

Relevant Anatomy

Anorectal disorders affect the perianal area (the portion of the skin

immediately surrounding the anus), the anal canal, and the lower portion of the rectum (Figure 17–1). The anal canal is approximately 2–4 cm long and connects the rectum with the outside of the body.¹ Two different types of epithelia line the anal canal; their junction is defined by the dentate line (also known as the pectinate line). The dentate line divides squamous epithelium from columnar epithelium, thus localizing sensory pain fibers in the anal canal.¹ Anorectal disorders occurring below the dentate line may be associated with pain, whereas disorders above the line rarely cause any discomfort.¹ The area proximal to the dentate line contains several longitudinal folds known as the columns of Morgagni.¹ In between and next to these columns are small pockets or crypts containing ducts and glands that may become obstructed and/or undergo other pathologic changes to cause infection (e.g., abscesses, fistulas).



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Figure 17–1 Disorders of the anorectal canal.

FIGURE 17–1 Disorders of the anorectal canal.

The external anal sphincter is a voluntary muscle located at the end of the anal canal that remains closed under normal conditions to prevent involuntary passage of feces. The internal sphincter is an involuntary muscle innervated by the autonomic nervous system.¹ When the sphincters are relaxed, defecation occurs. In healthy persons, mucosa covering the anal canal serves as a barrier

against absorption of substances into the body. If the protective barrier breaks, the absorptive properties of the anal skin may be altered, diminishing its protective capabilities.

The rectum, which lies above the anal canal, is approximately 12–15 cm long and constitutes the terminal portion of the large intestine.¹ The highly vascular rectal mucosa is lined with a semipermeable membrane to protect the body from fecal bacteria. Three hemorrhoidal arteries and their accompanying veins are the most prominent parts of the vasculature. Blood returns to the heart through the hemorrhoidal veins; therefore, rectal medications may be absorbed and enter the systemic circulation without passing through the liver.¹

Hemorrhoids

Hemorrhoids are conglomerations of inflamed, swollen blood vessels and other tissue that project into the bowel lumen during defecation.^{2,6,8} With increasing age or poor bowel habits (e.g., prolonged sitting and straining at defecation), muscle fibers weaken, causing the vascular cushions to slide, become congested, bleed, and eventually protrude.² Downward pressure during defecation and a high resting anal pressure are common contributory factors in the development of hemorrhoids.²

Internal hemorrhoids originate from the superior hemorrhoidal vein and are located above the dentate line, an area that is covered with columnar epithelium and lacks sensory fibers (Figure 17–1).^{2,6} Internal hemorrhoids are graded by severity of prolapse into the anal canal, as follows^{2,6}:

- Grade 1 hemorrhoids enlarge but do not prolapse into the anal canal.
- Grade 2 hemorrhoids protrude into the anal canal on defecation and retract spontaneously afterward.
- Grade 3 hemorrhoids protrude into the anal canal on defecation but can be returned to their original position manually.
- Grade 4 hemorrhoids are permanently prolapsed and cannot be reintroduced into the anus.

External hemorrhoids develop from the inferior hemorrhoidal vein and originate below the dentate line (Figure 17–1).² These hemorrhoids are classified either as nonthrombosed, in which the affected blood vessels are

pink and symptoms and signs may include bleeding and/or itching, or as thrombosed, in which the hemorrhoid has a purple-blue hue and often is associated with pain.²

Nonhemorrhoidal Anorectal Disorders

Potentially serious nonhemorrhoidal anorectal disorders (e.g., abscesses, fistulas, fissures, anal carcinoma) may manifest with hemorrhoid-like symptoms. With these disorders, self-treatment is not an option; referral for immediate medical evaluation is warranted (Table 17-1).^{1-3,9,10}

Table 17-1 Nonhemorrhoidal Anorectal Disorders

Disorder	Definition	Common Signs and Symptoms	Comments
Anal abscess	Collection of pus causing an obstruction of the anal glands, resulting in a bacterial infection	Pain, perirectal swelling, discharge, fever, or chills; pain worsens with sitting and defecation	Possible life-threatening sepsis if not identified and treated promptly
Anal fistula (or groove)	Abnormal internal opening that connects with an external opening (i.e., tubelike appearance between the rectum and anus)	Chronic, persistent drainage; pain; possible bleeding on defecation; perianal itching; seepage of stool through external opening	Surgical repair required
Anal fissure	Slitlike ulcer in anal canal resulting from a traumatic tear during passage of stool or explosive diarrhea	Severe or burning pain during and after defecation, lasting several minutes to hours; anal spasms; blood may be seen on toilet tissue	Young or middle-aged individuals affected; equal frequency in women and men
Anal neoplasms	Include a variety of histologic types classified as epidermoid carcinomas	Rare and usually asymptomatic in 25% of patients; bleeding; changes in bowel habits; anal discharge; anal mass; pain; pruritus; rash	Relatively uncommon, accounting for 4% of all GI malignancies; most are curable, but poor prognosis with anorectal melanomas
Pruritus ani	Itching sensation localized to anorectal area	Persistent itching, scratching in perianal region; more bothersome	More common in men, more than 100 recognized etiologic

Disorder	Definition	Common Signs and Symptoms	Comments
		at bedtime or when patient is not preoccupied	disorders

Key: GI = Gastrointestinal.

Source: References 1, 2, 14, and 19; and National Cancer Institute. Anal Cancer Treatment (PDQ®)-Health Professional Version. Available at: <https://www.cancer.gov/types/anal/hp/anal-treatment-pdq>. Accessed May 11, 2019.

Clinical Presentation of Anorectal Disorders

The U.S. Food and Drug Administration (FDA) Advisory Review Panel has identified signs and symptoms for which a nonprescription anorectal product is indicated.¹¹ These ailments include itching, discomfort, irritation, burning, soreness, inflammation, pain, dry anal tissue, and swelling in the perianal area.¹¹ By contrast, abdominal pain, bleeding, seepage, change in bowel patterns, prolapse, and thrombosis may indicate a more serious condition and necessitate immediate medical referral ([Table 17-2](#)).¹²

Table 17-2 Signs and Symptoms of Anorectal Disorders

Sign/ Symptom	Definition/Etiology
Usually Self-Treatable	
Itching (pruritus)	Mild stimulation of sensory nerve fibers; associated with many anorectal disorders, including hemorrhoids (typically with a mucoid discharge from prolapsing internal hemorrhoids).
	Common causes include poor hygiene (e.g., incomplete wiping/cleaning after defecation); diarrhea; parasitic or fungal infections; allergies (e.g., sensitivity to fabrics, soaps, laundry detergents, dyes, perfumes in toilet tissue); anorectal lesions; and moisture in anal area.
	May be secondary to swelling; diet (e.g., caffeinated beverages, chocolate, citrus fruits); or oral broad-spectrum antibiotics.

Sign/ Symptom	Definition/Etiology
	Rarely, may be of psychogenic origin.
Discomfort	May result from burning, itching, pain, irritation, inflammation, and swelling.
Irritation	Uncomfortable feeling associated with stimulation of sensory nerve fibers.
Burning	Greater degree of irritation of sensory nerve fibers than what is commonly experienced with anal itching; often associated with hemorrhoids; sensation of warmth or intense heat. May be constant or occur only on defecation.
Inflammation	Tissue reaction characterized by heat, redness or discoloration, pain, and swelling; often associated with trauma, allergy, or infection.
Swelling	Temporary enlargement of cells and/or tissue resulting from excess fluid; may be accompanied by pain, burning, and itching.
Necessitating Medical Referral	
Pain	Intense stimulation of sensory nerve fibers caused by inflammation or irritation. Internal hemorrhoids usually are painless; external hemorrhoids often cause mild to moderate pain; acute, severe perianal pain may be from a thrombosed external hemorrhoid. Pain from anal fissure during bowel movement often described as “being cut with sharp glass.”
	Other possible causes of pain include abscess, fistula, or anorectal neoplasm.
Bleeding	Hemorrhoids most common cause of minor bleeds (e.g., from straining or passage of hard stool, or ulceration of perianal skin overlying thrombosed external hemorrhoid).
	Appears as bright red spots or streaks on toilet tissue, or bright red blood around stool or in toilet.
	Black or tarry stools (melena) may indicate possible upper GI bleeding (e.g., from peptic ulcer disease, erosive esophagitis, or gastric varices).
	Large amounts of red blood (hematochezia) in toilet bowl indicative of lower GI bleeding (e.g., from fissure, inflammatory bowel disease, polyps, or malignant disease of the colon or rectum).
	Possible indications of large-volume blood loss include shortness of breath, dizziness, fatigue, and light-headedness, especially upon standing (orthostatic hypotension).
Seepage	Involuntary passage of fecal material or mucus through an incompletely closed anal

Sign/ Symptom	Definition/Etiology
	sphincter, or discharge of pus or feces from a fistula connecting the rectum to the anal canal.
Change in bowel pattern	Unexplained change in bowel frequency or in stool form; may signal serious underlying GI disorder (e.g., IBD) or colorectal cancer.
Prolapse (protrusion)	Protrusion of hemorrhoidal or rectal tissue of variable size into anal canal; usually appears after defecation, prolonged standing, unusual physical exertion, or swelling of hemorrhoidal tissue with loss of muscular support; painless except when accompanied by thrombosis, infection, or ulceration.
Thrombosis	Strangulation of protruded (external) hemorrhoid by anal sphincter, possibly leading to thrombosis; pain is most acute during first 48–72 hours but usually resolves after 7–10 days.
	Minimal pain with thrombosed internal hemorrhoids; patient likely to be unaware of condition unless sudden change in bowel habits occurs.
	If a thrombosed hemorrhoid persists, ulcers or gangrene may develop and cause bleeding, especially during defecation.

Key: GI = Gastrointestinal; IBD = inflammatory bowel disease; PUD = peptic ulcer disease.

Source: [References 15](#) and [18](#); and Summers A. Anorectal examination in emergency departments. *Emerg Nurse*. 2013;21(1):21–6. PMID: 23691894.

Algorithm: Hemorrhoids

Figure 17–2 Self-care for hemorrhoids. Key: CAM = Complementary and alternative medicine; CVD = cardiovascular disease; GI = gastrointestinal; HTN = hypertension; PCP = primary care provider.

Treatment of Anorectal Disorders

Treatment Goals

The primary goal of treatment for anorectal disorders is to resolve associated symptoms of pain, discomfort, and burning. Maintaining soft stools and preventing straining during a bowel movement are paramount in minimizing anorectal symptoms^{13–16} (see [Chapter 15](#)). Additional goals are to maintain remission of anorectal symptoms and to prevent complications.

General Treatment Approach

[Figure 17–2](#) presents an algorithm for self-care for minor anorectal symptoms and lists exclusions for self-treatment. If symptoms qualify for self-treatment, then the health care provider may recommend nonpharmacologic measures and a nonprescription agent to treat the symptoms. Patients should be advised to maintain adequate fluid intake and a well-balanced, high-fiber diet. Practicing good perianal hygiene and avoiding prolonged sitting on the toilet also may minimize anorectal symptoms.^{13–16} [Table 17–3](#) outlines guidelines for applying anorectal products.^{11,17}

Table 17–3 Guidelines for Applying or Inserting Anorectal Products

- Wash hands before and after application of any anorectal product.
- Empty bladder and bowels before using any anorectal product, if possible.
- Clean affected anorectal area after bowel movement with mild, nonmedicated, unscented soap and warm water; rinse thoroughly.
- Clean anorectal area before applying products containing aluminum hydroxide gel or kaolin. Be sure to remove any previously used petrolatum-containing or greasy ointment.^a
- Dry anorectal area gently by patting or blotting with unscented and uncolored toilet tissue or a soft cloth before applying product.
- Apply a thin layer to the perianal area and anal canal when using an external anorectal product.
- Insert anorectal products indicated for intrarectal use by using an intrarectal applicator or a finger. Intrarectal applicators are preferred to digital application because use of an applicator allows application of the drug product to the rectal mucosa (which cannot be reached with a finger)
- Clean anorectal applicator per product instructions between uses.
- Ensure that intrarectal applicators have lateral openings and holes in the tip to facilitate anorectal application and coverage of the rectal mucosa with inserted product.
- Lubricate intrarectal applicator by spreading product around the applicator tip before insertion into the anorectal area.
- Avoid using the intrarectal applicator in the anorectal area if it causes additional pain.

- Do not exceed the recommended daily dosage unless directed by a primary care provider.

^a *Ointment* refers to all semisolid preparations. Source: References 19, 30, and 31.

Nonpharmacologic Therapy

Nondrug measures for treating anorectal disorders include dietary modifications, surgical interventions, and nonoperative methods.^{2,13–16} Patients diagnosed with or suspected of having hemorrhoids should avoid lifting heavy objects and discontinue foods that aggravate symptoms (e.g., alcohol, caffeinated beverages, citrus, fatty foods).¹⁵

Dietary fiber softens stool and may prevent further irritation of symptomatic hemorrhoids and other anorectal disorders. A high-fiber diet (25–40 g of fiber per day) will help prevent bleeding and contribute to overall symptomatic anorectal relief by permitting the passage of softer stools, thereby reducing and preventing irritation and straining at defecation.^{15,18,19} Dietary fiber intake should be increased slowly; however, if the intake amount cannot be increased, fiber supplements such as psyllium or methylcellulose can be considered (see [Chapter 15](#)). Additionally, it is important for patients to drink an adequate amount of noncaffeinated fluid (daily intake of 8 eight-ounce cups) to soften hard stool.¹⁸

Proper bowel habits should be identified and encouraged. Suppressing or ignoring the urge to defecate should be discouraged because doing so may lead to constipation, resulting in anorectal discomfort. Limiting time sitting on the toilet to 2–5 minutes reduces strain and decreases prolonged pressure on the hemorrhoidal vessels.^{16,18,19} Proper hygiene of the anal area (e.g., cleaning the area regularly, but not excessively, after each bowel movement using mild, unscented soap and water) may help relieve anorectal symptoms.^{18,19} Use of commercially available hygienic and lubricated wipes or pads is not recommended because they may be more irritating to the anal area, especially in patients with pruritus ani.¹⁹ Excessive scrubbing should be discouraged to minimize aggravation.^{2,19} A nonpharmacologic measure often recommended to promote good anal hygiene and to reduce pain and itching, despite a lack of supporting evidence, is sitting in warm water ($\leq 120^{\circ}\text{F}$ [48.89°C]) in a bathtub or

sitz bath (a small basin that fits over the toilet rim, available at pharmacies and medical supply vendors) for 10–20 minutes 2–4 times a day.^{18,20} In a few systematic reviews of randomized controlled trials, no evidence supported the use of sitz baths to relieve pain or assist in wound healing in patients with anorectal disorders; however, health care providers commonly recommend this option.²⁰

Large and prolapsed hemorrhoids (grade 3 or 4) often are treated surgically. Accordingly, patients with more severe hemorrhoids usually are referred to a colorectal specialist for further evaluation.^{14–16}

Pharmacologic Therapy

Local anesthetics, vasoconstrictors, protectants, astringents, keratolytics, analgesics, anesthetics, antipruritics, and corticosteroids are commonly used to relieve anorectal symptoms.¹¹ Certain astringents, protectants, and vasoconstrictors may be used only intrarectally and should be administered with an applicator (i.e., “pile pipe”) so that the product can reach the affected area.¹¹ Use of suppositories may be considered as another method of administering a drug to the anal area; however, their effectiveness is in question, as suppositories may not stay in place after insertion. The remaining agents—local anesthetics, keratolytics, analgesics, anesthetics, and antipruritics—are for external use only and are not indicated for the relief of anorectal pain, bleeding, seepage, prolapse, or thrombosis.¹¹ **Table 17–4** provides FDA-approved dosages for anorectal drug products.¹¹

Table 17–4 Dosage Guidelines for Anorectal Products		
Ingredient	Concentration per Dosage Unit (%)	Frequency of Use (with maximum daily dosage)
Local Anesthetics		
Benzocaine	5–20	Up to 6 times/day (2.4 g)
Benzyl alcohol	1–4	Up to 6 times/day (480 mg)
Dibucaine, dibucaine hydrochloride	0.25–1	Up to 3–4 times/day (80 mg)
Dyclonine hydrochloride	0.5–1	Up to 6 times/day (100 mg)

Ingredient	Concentration per Dosage Unit (%)	Frequency of Use (with maximum daily dosage)
Lidocaine	2-5	Up to 6 times/day (500 mg)
Pramoxine hydrochloride ^a	1	Up to 5 times/day (100 mg)
Tetracaine, tetracaine hydrochloride	0.5-1	Up to 6 times/day (100 mg)
Vasoconstrictors		
Ephedrine sulfate	0.1-1.25	Up to 4 times/day (100 mg)
Epinephrine, epinephrine hydrochloride	0.005-0.01	Up to 4 times/day (800 mg)
Phenylephrine hydrochloride	0.25	Up to 4 times/day (2 mg)
Protectants		
Aluminum hydroxide gel, cocoa butter, glycerin, hard fat, kaolin, lanolin, mineral oil, white petrolatum, calamine, ^c petrolatum, shark or cod liver oil, ^d zinc oxide, ^e topical starch, white petrolatum	See footnote b.	Petrolatum/white petrolatum as often as needed; other protectants up to 6 times/day or after each bowel movement
Astringents		
Calamine ^c	5-25	Up to 6 times/day or after each bowel movement
Zinc oxide	5-25	Up to 6 times/day or after each bowel movement
Witch hazel	10-50	Up to 6 times/day or after each bowel movement
Keratolytics		
Alcloxa	0.2-2	Up to 6 times/day
Resorcinol	1-3	Up to 6 times/day
Analgesics, Anesthetics, Antipruritics		
Menthol	0.1-1	Up to 6 times/day
Juniper tar	1-5	Up to 6 times/day

Ingredient	Concentration per Dosage Unit (%)	Frequency of Use (with maximum daily dosage)
Camphor	0.1-3	Up to 6 times/day
Corticosteroids		
Hydrocortisone	0.25-1	Up to 3-4 times/day

^a External dosage forms may include aerosol foams, ointments, creams, and jellies (water-miscible base).

^b Any two, three, or four protectants may be combined, provided that the combined percentage by weight of all protectants in the combination is at least 50% of the final product. Any protectant ingredient included in the combination must be present at a level that contributes at least 12.5% by weight (e.g., 0.25 g of a 2-g dosage unit), except for cod liver oil and shark liver oil. If cocoa butter is included in the combination, it must not exceed the concentration limit for calamine,^c cod liver oil,^d or shark liver oil.^d

^c Calamine not to exceed 25% by weight per dosage unit (based on the zinc oxide content of calamine).

^d Provided that the product is labeled so that the amount of the product that is used in a 24-hour period represents a quantity that provides 10,000 USP units of vitamin A and 400 USP units of cholecalciferol.

^e Any product containing calamine or zinc oxide for use as a protectant and/or as an astringent may not have a total weight of zinc oxide exceeding 25% by weight per dosage unit.

Key: USP = United States Pharmacopeia.

Source: Reference 11.

Local Anesthetics

Local anesthetics are approved for the temporary relief of external anal symptoms (e.g., itching, irritation, burning, discomfort, soreness, and pain); they provide relief by reversibly blocking transmission of nerve impulses (Table 17-4).^{11,17} Caution is advised with use of these products because they may mask the pain of more severe anorectal disorders.¹⁷

Local anesthetics may produce allergic reactions (e.g., burning, itching) that are indistinguishable from the anorectal symptoms. Several cases of contact dermatitis associated with hemorrhoidal anesthetics have been reported.²¹⁻²³ Patients who have an allergic reaction to a local anesthetic may try another agent with a different chemical structure (e.g., pramoxine) or avoid such agents completely. These preparations must carry a warning stating that allergic reactions may occur.¹¹ Local anesthetics should be avoided on open sores because they are rapidly absorbed through abraded skin, with the potential for cardiovascular and central nervous system effects. Accidental oral ingestion of dibucaine-containing anorectal products has been reported in children, resulting in lethargy, seizures, and cardiorespiratory arrest; these products should be kept out of children's reach.^{23,24}

Vasoconstrictors

Topical vasoconstrictors (ephedrine, epinephrine) are structurally related to the endogenous catecholamines epinephrine and norepinephrine. With application to the anorectal area, stimulation of α -adrenergic receptors in the vascular beds constricts arterioles, producing a modest and transient reduction of swelling. These agents are indicated ([Table 17-4](#)) for relief of itching, discomfort, and irritation and to shrink and decrease swelling of the hemorrhoidal tissues.¹¹ Ephedrine sulfate and phenylephrine HCl are safe and effective for external and intrarectal use, and epinephrine or epinephrine HCl is approved for external use only.¹¹

Adverse effects of ephedrine and epinephrine include increased cardiac rate and contractility, as well as bronchodilation, if absorbed systemically. By contrast, because phenylephrine HCl is structurally related to norepinephrine, effects on the central nervous system and cardiac rhythm are minimal. When used in recommended topical dosages, ephedrine sulfate may cause nervousness, tremors, sleeplessness, nausea, and loss of appetite.¹¹ Serious adverse effects (e.g., elevation of blood pressure, aggravation of hyperthyroidism, cardiac arrhythmias, irregular heart rate) are less likely to occur with topical than with oral administration.¹⁷ Prolonged use may lead to rebound vasodilation, anxiety, and (rarely) paranoia. Contact dermatitis also may occur.

Rectally administered vasoconstrictors may attenuate the effects of oral antihypertensive agents and increase blood pressure. Alternatively, the

hypertensive effects of vasoconstrictors may be potentiated by monoamine oxidase inhibitors and tricyclic antidepressants which may lead to serious and even lethal outcomes, including cerebral hemorrhage or stroke.¹⁷ Patients with diabetes, thyroid disease, heart disease, or hypertension, or those having difficulty with urination due to an enlarged prostate, as well as those taking antidepressants, antihypertensive agents, or cardiac medications, should first consult with their primary care provider before using these vasoconstrictors.¹¹

Protectants

Protectants are ingredients that provide a physical protective barrier over inflamed anal tissue and soften the lining of the anal canal by preventing fecal matter from irritating or drying the perianal mucosa.¹¹ This drug class includes absorbents, adsorbents, demulcents, and emollients. Approved indications for most protectants include the temporary relief of discomfort, irritation, and burning with external and internal hemorrhoids (one exception is glycerin, which is for external use only) ([Table 17–4](#)).¹¹ Kaolin and aluminum hydroxide gel are indicated for the temporary relief of itching associated with moist anorectal conditions.¹¹

Systemic absorption of protectants is minimal; therefore, adverse reactions to agents of this class are uncommon. Lanolin is a natural product obtained from the fleece of sheep, so it may cause allergic reactions.¹¹ Chemically modified lanolin is available and may be less sensitizing.

A warning statement for aluminum hydroxide gel and kaolin products states that any greasy ointments or petrolatum-based products should be removed before application so that the protectant can adhere properly to the anorectal skin area.¹¹

Astringents

Astringents are products that promote coagulation of surface protein in the anorectal skin cells to protect the underlying tissue. Astringents also act to decrease cell volume, making the affected anorectal environment drier to prevent further irritation, and form a thin protective layer over the injured mucosal membrane.¹¹ Astringents listed in [Table 17–4](#) are approved for the temporary relief of itching, irritation, and burning symptoms associated with anorectal disorders.¹¹ Witch hazel (known as hamamelis water before January 1,

1995) is indicated for external use, whereas calamine and zinc oxide may be used for external and internal anorectal disorders.¹¹

Adverse effects with the topical use of astringents are uncommon. Upon application, witch hazel may cause a slight stinging sensation from the alcohol, or contact dermatitis may result from the small amount of volatile oil used to prepare the compound. If calamine or zinc oxide is used for prolonged periods of time (especially for internal anorectal disorders), systemic zinc toxicity (nausea, vomiting, lethargy, and/or severe pain), although rare, may develop.¹¹

Keratolytics

Keratolytics are agents that cause desquamation and debridement (or sloughing) of epidermal surface cells. By fostering cell turnover and loosening surface cells, low concentrations of keratolytics may expose the underlying tissue. When other anorectal ingredients are used in combination with keratolytics, they reduce itching and inflammation ([Table 17-4](#)).¹¹ Because mucous membranes do not contain a keratin layer, intrarectal use of keratolytics is not justified and may be harmful.^{11,17}

With repeated dosing, the absorption of the keratolytic resorcinol has led to methemoglobinemia, exfoliative dermatitis, death in infants, and myxedema in adults.¹⁷ Other adverse effects range in severity from tinnitus, increased pulse rate, diaphoresis, and shortness of breath to circulatory collapse, unconsciousness, and seizures. Products containing resorcinol must include the following warnings to minimize absorption through abraded mucosal lining and to decrease the potential for systemic toxicity: (1) “Certain persons can develop allergic reactions to ingredients in this product. If the symptoms being treated do not subside, or if redness, irritation, swelling, pain, or other symptoms develop or increase, discontinue use and consult a doctor.” (2) “Do not use on open wounds near the anus.”¹¹ Although keratolytics are available in selected anorectal preparations, the potential benefit must be weighed against their potentially serious adverse effects.

Analgesics, Anesthetics, and Antipruritics

Formerly classified as “counterirritants,” menthol, juniper tar, and camphor are safe and effective when used for external perianal disorders. These agents

(Table 17–4) are approved for the temporary relief of burning, pain, or itching by producing a cool, warm, or tingling sensation.¹¹ These agents should not be used internally because the rectum has no identifiable nerve fibers. Menthol-containing products must carry the following warning: “Certain persons can develop allergic reactions to ingredients in this product. If the symptoms being treated do not subside, or if redness, irritation, swelling, pain, or other symptoms develop or increase, discontinue use and consult a doctor.”¹¹ Extensive application of menthol to the trunk of the body has caused laryngospasm, dyspnea, and cyanosis; therefore, menthol should be used only sparingly.¹⁷ Juniper tar, which contains phenol, also should be used sparingly; and it should not be ingested orally because organ failure and cardiac rhythm abnormalities may result.²⁵ Camphor is readily absorbed through mucous membranes and stimulates the central nervous system, which may lead to convulsions or death. Fatalities have occurred mostly with accidental oral ingestion, especially in children.¹⁷

Corticosteroids

Approximately 60% of the topical anorectal agents contain hydrocortisone, which acts as a vasoconstrictor and antipruritic by producing lysosomal membrane stabilization and antimitotic activity.²⁶ The onset of action may take up to 12 hours, but the effect has a longer duration than that of most other agents (e.g., local anesthetics). Hydrocortisone, in concentrations of no more than 1%, is the only corticosteroid approved for nonprescription use in anorectal preparations for the temporary relief of minor external anal itching caused by minor irritation or rash.²⁷ Local adverse effects include rare skin reactions and skin atrophy with prolonged use. Hydrocortisone also may mask the symptoms of bacterial and fungal infections.

Combination Products

Federal regulations state that a nonprescription anorectal product may combine two or more active ingredients; combination products generally are recognized as safe and effective when (1) each active ingredient contributes to the claimed effect; (2) the combination of active ingredients does not decrease the safety or effectiveness of any individual active ingredient; and (3) the combination, with adequate directions for use and warning against unsafe use, provides rational, concurrent therapy for a significant proportion of the target population.^{11,17} FDA restrictions on combination anorectal products can

be found by accessing the *Federal Register*.¹¹ Use of combination products is reasonable in that some self-treatable anorectal disorders may be associated with concurrent symptoms. However, a combination of active ingredients has not been shown to be any more effective than a preparation containing a therapeutic amount of a single agent.^{11,17} Additionally, restricting the number of ingredients should decrease the risk of interactions and adverse drug reactions.²⁶

Product Selection Guidelines

Table 17–5 contains examples of products by category that can be recommended for hemorrhoids.

Table 17–5 Selected Nonprescription Products for Hemorrhoids	
Trade Name	Primary Ingredient(s)
Local Anesthetics	
Americaine Ointment ^a	Benzocaine 20%
Nupercainal Hemorrhoidal Ointment	Dibucaine 1%
Tronolane Anesthetic for Hemorrhoids ^b	Pramoxine HCl 1%; zinc oxide 5%
Vasoconstrictors	
Preparation H Cooling Gel ^c	Witch hazel 50%; phenylephrine HCl 0.25%
Preparation H Suppositories ^c	Phenylephrine HCl 0.25%; cocoa butter 88.44%
Skin Protectants	
Preparation H Ointment ^c	Mineral oil 14%; petrolatum 74.9%; phenylephrine HCl 0.25%
Hydrocortisone Products	
Preparation H Anti-Itch Cream Hydrocortisone 1% ^c	Hydrocortisone 1%
Miscellaneous and Combination Products^e	
Preparation H Maximum Strength Pain Cream ^c	Glycerin 14.4%; phenylephrine HCl 0.25%; pramoxine HCl 1%; white petrolatum 15%

Trade Name	Primary Ingredient(s)
Preparation H Medicated Wipes ^c	Witch hazel 50%
Preparation H Totables Irritation Relief Wipes ^c	Witch hazel 50%
Preparation H Medicated Wipes for Women ^c	Witch hazel 20%
TUCKS Medicated Cooling Pads ^c	Witch hazel 50%
Preparation H Rapid Relief ^c	Lidocaine 5%; glycerin 14.4%
Calmol 4 Hemorrhoidal Suppositories ^d	Cocoa butter 76%; zinc oxide 10%

^a Source: Dailymed website. Available at: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=d-13c022f-2f91-40b4-bd66-0cfc0e147a5f&type=display>. Accessed May 16, 2019.

^b Source: Tronolane Anesthetic for Hemorrhoids. Drugs.com. Available at: <https://www.drugs.com/mtm/tronolane-anesthetic-for-hemorrhoids.html>. Accessed May 16, 2019.

^c Source: Preparation H website. Available at: <http://www.preparationh.com>. Accessed May 16, 2019.

^d Source: Calmol 4 website. Available at: <http://resical.com/calmol-4-hemorrhoid-suppositories/label-information/>. Accessed August 16, 2019.

^e Currently, no U.S. Food and Drug Administration (FDA)-approved nonprescription product contains ephedrine sulfate

Knowledge of the patient's medical history, medication profile, and relevant socioeconomic factors is necessary to determine what product to recommend and how that patient may respond to self-treatment. Selection of a product should be based on (1) the type, location, and severity of the anorectal disorder; (2) diseases or significant past medical history; (3) current medications and nutritional supplements and/or herbal products; (4) allergies; (5) ability to apply or insert the medication (with consideration of physical, mental, and emotional

limitations); and (6) any other factors that may affect treatment (e.g., diet, daily activities, cost of the product).

Special Populations

The most common anorectal disorder in pregnancy is hemorrhoids.^{28,29} Approximately 25% of all pregnant females will complain of hemorrhoids, and this increases to 85% at the time of birth.²⁸ Pregnant and breastfeeding women should use products recommended for external use; an exception is those agents that act as protectants (but not those containing glycerin), which may be used internally. Nonpharmacologic interventions, including increasing dietary fiber and fluid intake to minimize constipation, may be beneficial throughout pregnancy and the postpartum period.²⁸

Anorectal disorders in children younger than 12 years are not common, and patients should be referred to a specialist for further medical evaluation.^{11,29,30} Because constipation is more common in the older population, these patients may be more prone to development of hemorrhoids.^{28,29} Of note, patients who are older than 40 years and have rectal bleeding or a positive family history of colon cancer should be evaluated for colorectal carcinoma.^{15,29} Additionally, patients with a family history of inflammatory bowel disease (i.e., Crohn's disease, ulcerative colitis) should be referred for medical evaluation.¹⁵ Otherwise, treatment for persons in any special population is similar to treatment for an adult patient.

Patient Factors

FDA does not require comparison trials between combination and individual products, so therapeutic differences have not been established. However, when used to treat anorectal symptoms for the preceding FDA indications, combination products containing approved ingredients in appropriate dosages are most likely therapeutically similar to individual drug products.^{11,17} Any perceived differences probably are related to personal preference for a specific product or dosage form. Using more than one product, or a product containing multiple ingredients, is reasonable because patients may have multiple symptoms that may not be adequately addressed by one product alone.^{11,17}

Medications used to treat anorectal disorders are available in many dosage forms. Creams, suppositories, gels, pastes, liquids, foams, and ointments are

primarily used externally. However, the term *ointment* used in this chapter refers to all semisolid preparations designed for intrarectal or external use in the anorectal area for its protectant and emollient properties. Additionally, ointments may be used to provide a vehicle for the safe and efficient delivery of the active ingredients.

Applicators, intrarectal applicators, or the patient's fingers can be used to apply anorectal preparations. Considerable pharmaceutical differences among the various dosage forms are recognized, but no clinical differences have been established.¹¹

Suppositories are solid dosage forms that deliver drugs into body orifices, typically in the anorectal area.^{17,31} Suppositories should not be recommended as an initial dosage form because they may leave the affected anal region and ascend into the rectum and lower colon when the patient is in an upright position.^{13,31} If the patient remains upright after insertion of a suppository or ointment, the active ingredients may not distribute evenly over the anal mucosa. Therefore, after insertion, the patient should lie on the left side with knees bent so that the preparation remains in the affected area for at least 15–20 minutes.³² Suppositories have a relatively slower onset of action than with other dosage forms because the solid product must dissolve to release the active ingredients (see [Chapter 15](#)). To prolong retention rates in the anorectal area, some health care providers recommend introducing the base of the suppository first, rather than the tapered end.³¹ A suppository that is too soft to administer can be hardened in the refrigerator for at least 30 minutes before use.³¹

Foam products theoretically should provide more rapid release of active ingredients compared with ointments.¹⁷ Foams are more expensive than ointments, however, and do not offer any specific advantage. Also, foams may not remain in the affected area, and differences in the size of the foam bubbles may result in variable concentrations of the active ingredient.¹⁷

Complementary Therapies

The use of dietary supplements, including herbal products, to manage hemorrhoids has not been researched properly, although evidence of benefit has been reported for several preparations.³³

The combination of diosmin and hesperidin (a micronized purified flavonoid fraction) has been used to stop acute bleeding and decrease symptoms associated with hemorrhoids.^{34,35} The mechanism of action is still in question, but animal models suggest that this product inhibits prostaglandin and thromboxane mediators, thereby decreasing the inflammation.³⁵ The combination appears to be safe when taken orally for less than 6 months, with the most common adverse effects being headache, muscle cramps, asthenia, abdominal pain, diarrhea, and gastritis.³⁵ Although rare, allergic dermatitis may occur if such preparations are applied topically.³⁵ Diosmin administered in lower doses with a bulk laxative has some effect on reducing symptoms of hemorrhoids, but its efficacy is greater when given with hesperidin.³⁶ Common adverse effects associated with diosmin include abdominal pain, diarrhea, gastritis, headache, and dizziness. Dermatologic and cardiac symptoms including arrhythmias as well as hemolytic anemia have also been rarely observed.³⁶

Horse chestnut seed extract (HCSE) has been used to support the management of hemorrhoids.³⁷ When HCSE is processed properly and used for less than 3 months, it is relatively safe, with adverse effects including itching, nausea, and vomiting. Improperly prepared HCSE preparations, especially with ingestion of raw seed, bark, flower or leaf, may be poisonous, with the potential for fatal reactions.³⁷

Assessment of Anorectal Disorders: A Case-Based Approach

To accurately assess whether the anorectal disorder is amenable to self-treatment, the health care provider should obtain a thorough description of the patient's signs and symptoms. Other important information to ascertain before recommending self-treatment includes the presence of certain concomitant diseases (e.g., hypertension, diabetes, benign prostatic hyperplasia, psychiatric illness); the patient's current or recent prescription and nonprescription medications, including nutritional supplements and complementary and alternative medicine preparations; and diet, lifestyle, and exercise factors.

Cases 17-1 and 17-2 illustrate assessment of anorectal disorders in two different

patients.

Case 17-1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient, who is pregnant, complains of burning, itching and some blood on toilet paper after having a bowel movement, which started in her third trimester. She also describes a feeling of pressure in the "bottom."
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Bowel movement causes pain and discomfort. Stool usually is hard, but when it is soft, symptoms are less severe. Drinking water and eating greens help with symptoms.
c. Description of the patient's efforts to relieve the symptoms	Not sitting on toilet for longer than 10 minutes
d. Patient's identity	Jenny Nok
e. Patient's age, gender, height, and weight	32 years, female, 5 ft 4 in., 166 lb
f. Patient's occupation	Surgical ICU nurse

g. Patient's dietary habits	Eats meat daily with minimal fruits and vegetables. Fluid intake has been decreased recently.
h. Patient's sleep habits	6-7 hours nightly
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Healthy. Prenatal multivitamin daily, folate acid 1 mg daily, docusate sodium twice daily.
j. Allergies	Sulfa
k. History of other adverse reactions to medications	None
l. Other (describe) -----	Patient exercise has diminished as she continues into the pregnancy.

Assess

2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s) (Tables 17-1 and 17-2).	Ms. Nok may have anorectal symptoms, including those due to hemorrhoids and pruritus ani, as her diet and exercise regimen has changed, thus causing her to have hard stools and having to increase pressure while defecation.
3. Identify exclusions for self-treatment (Figure 17-2).	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required and share this information with	Options include (1) Recommend self-care with an appropriate OTC anorectal product and advise on nondrug measures. (2) Recommend self-care with an appropriate OTC anorectal product and advise on nondrug measures until patient can contact her primary care or other health care provider.

the patient or caregiver.	(3) Refer patient to her primary care provider for further evaluation of her symptoms. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	The second option is the best: self-care and nondrug measures until the patient can contact her primary care provider. Recommend an external hemorrhoidal agent only. If internal-use agents are preferred, recommend products with protectants (except glycerin). Recommend patient increase fluid intake (water), dietary fiber (fruits, vegetables), and, if possible, exercise. Sitz baths used 3 times a day may resolve anorectal symptoms. Encourage patient to wear soft, loose-fitting clothing. Also educate patient to use unscented, undyed (white) toilet paper and to use gentle technique in wiping the anal area.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Your symptoms, including itching, pain, and bleeding, may be related to hemorrhoids and anal itching. The hemorrhoids may have developed as the baby continues to grow, which causes pressure in the anal area. The changes in your body with pregnancy cause increased internal pressure, especially during a bowel movement, which may produce hemorrhoids. I'm recommending you use a self-care product for now; however, you should contact your primary care provider for further evaluation in a few days if your symptoms do not decrease or resolve."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"If symptoms do not resolve in a week, seek medical attention. Although your symptoms, including having bowel movement discomfort, pain, and anal itching, may be related to hemorrhoids, you should contact your primary care provider or OB/GYN specialist for further evaluation. Other conditions also may cause similar symptoms."
Implement	
8. When recommending self-care with	

nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
a. Appropriate dose and frequency of administration	See Table 17-4 .
b. Maximum number of days the therapy should be employed	“Contact your primary care provider if after 7 days the symptoms do not resolve. Be sure to let your provider know what self-care measures you have taken.”
c. Product administration procedures	See Table 17-3 .
d. Expected time to onset of relief	“The irritation, burning, and discomfort may be relieved within a few days of applying the topical agent as directed.” Advise the patient to avoid straining and to drink adequate fluids and eat a healthy diet that is high in dietary fiber. “If required, keep using the stool softener, or add a fiber supplement, as needed. Although the bleeding may stop with treatment, be sure to contact your primary care provider for further evaluation.”
e. Degree of relief that can be reasonably expected	“Your anorectal symptoms should resolve a few months after giving birth.”
f. Most common adverse effects	“Products applied to the anal area are usually well tolerated.”
g. Adverse effects that warrant medical intervention should they occur	“If you develop an allergic reaction to the product, such as redness, swelling, increased irritation, or pain, discontinue use, and contact your primary care provider as soon as possible.”
h. Patient options in the event that condition worsens or persists	“If your symptoms worsen, contact your primary care provider as soon as possible.”
i. Product storage requirements	“Store medication out of the reach of children and at a controlled room temperature.”

j. Specific nondrug measures	"Practice good anal hygiene, use sitz baths, and consider increasing fluid intake. Incorporate an exercise regimen if possible."
Solicit follow-up questions from the patient or caregiver.	"Will this affect my baby?"
Answer the patient's or caregiver's questions.	"Probably not. If you practice good anal hygiene, use sitz baths, and increase fluid intake and exercise, your stools should be soft, so that the local stress of having a bowel movement will not irritate the anal canal. Use of the recommended product should not affect the baby."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Ask Ms. Nok to call to update you on her response to your recommendations. Alternatively, you could call her in a week to evaluate her response and make sure that she touched base with her primary care provider.
Key: OB-GYN = Obstetrics-gynecology; OTC = over-the-counter.	

Case 17-2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient complains of bleeding in the anal area for 1 week and seeing blood in the toilet bowl. Patient describes blood on the toilet paper with each wiping. He has a low-grade fever (temperature of 99.9°F [37.2°C]; oral). He has had these symptoms before but says the abdominal pain is new.
b. Description of any factors that seem to precipitate,	Symptoms are worst when he is unable to have a bowel movement. He states that the stomach pain, on a scale of

exacerbate, and/or relieve the patient's symptom(s)	1-10 (10 being worst), feels like a 6. He has not changed his diet or exercise regimen but has lost about 10 pounds in a few weeks.
c. Description of the patient's efforts to relieve the symptoms	The patient has tried topical hydrocortisone cream in the anorectal area without relief for the past 2 days.
d. Patient's identity	Matt Knowling
e. Patient's age, gender, height, and weight	28 years, male, 5 ft 8 in., 149 lb
f. Patient's occupation	Graduate student (master's degree program in business administration)
g. Patient's dietary habits	Eats healthy meals, including meat, fruits, and vegetables. Eats sweets while studying. Does not smoke. Drinks socially at parties.
h. Patient's sleep habits	5-6 hours nightly
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Acne diagnosed at age 21; takes a multivitamin daily.
j. Allergies	Penicillin (anaphylactic reaction)
k. History of other adverse reactions to medications	None
l. Other (describe) _____	Mr. Knowling's father is alive with colon cancer at the age of 56. His mother also is living and diagnosed with depression. He has a brother who has ulcerative colitis. He is single.
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s) (Tables 17-1 and 17-2).	Mr. Knowling experiences abdominal pain on defecation and has blood in his stool, along with low-grade fever. There is a family history of colon cancer and ulcerative colitis.
	He states that his diet, fluid, and exercise regimens have not changed, yet he has continued to lose weight over the past

	few weeks. Given that Mr. Knowling is in his late 20s and has a family history of colon cancer and a brother with ulcerative colitis, it is possible that he has an oncologic condition or IBD.
3. Identify exclusions for self-treatment (Figure 17-2).	Blood in toilet, abdominal cramping, experiencing pain with each bowel movement. Strong family history of colon cancer.
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required and share this information with the patient or caregiver.	Options include (1) Recommend self-care with an appropriate OTC anorectal product and advise on nondrug measures. (2) Recommend self-care with an appropriate OTC anorectal product and advise on nondrug measures until patient can contact his usual health care provider. (3) Refer patient to an appropriate health care provider for medical evaluation of his symptoms immediately. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Mr. Knowling should consult an appropriate health care provider immediately for medical evaluation to rule out bleeding from a source other than a hemorrhoid or anal fissures or fistulas. He is young and has significant abdominal pain with each bowel movement. Mr. Knowling may have colon cancer or IBD, because there is a strong family history of cancer and GI conditions (Figure 17-2).
6. Describe the recommended therapeutic approach to the patient or caregiver.	"You should consult a health care provider for immediate medical evaluation. I'm concerned about your symptoms and your family history."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic	"Because you tried using the hydrocortisone cream with no relief, the best option is for you to see your usual health care provider immediately. You have a strong family history of colon cancer and stomach issues. The signs and symptoms you are complaining about may be symptoms of IBD. Please

alternatives.	see your primary care provider to have your symptoms evaluated and testing done as soon as possible.”
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	Criterion does not apply in this case.
Solicit follow-up questions from the patient or caregiver.	“What is IBD?”
Answer the patient’s or caregiver’s questions.	“IBD is inflammatory bowel disease. This is not an unlikely cause of your symptoms because your brother has ulcerative colitis, a type of IBD. The way to determine if you have this medical condition is by seeing an appropriate specialist in gastrointestinal disorders to do more tests.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Mr. Knowing in 1-2 days to ensure that he made an appointment and sought immediate and appropriate medical care.
Key: IBD = Inflammatory bowel disease; GI = gastrointestinal; OTC = over-the-counter; PCP = primary care provider.	

Patient Counseling for Anorectal Disorders

The most appropriate drug and nondrug measures for treating specific anorectal signs and symptoms should be explained to the patient. Counseling should include dosage and frequency of administration, administration technique, onset of action, possible adverse effects, precautions or warnings, and product storage. Patients should understand when self-care should be discontinued and when to consult a primary care provider. If the topical nonprescription agents do not resolve the anorectal symptoms within 7 days, medical referral is appropriate.¹¹ Patients should be advised not to exceed the

recommended daily dosage unless their primary care provider recommends a higher dosage.¹¹ The box “Patient Education for Anorectal Disorders” lists specific information to provide in patient counseling.

Evaluation of Patient Outcomes for Anorectal Disorders

Self-treatment for anorectal disorders should be limited to management of minor symptoms. If serious or severe symptoms are present, or if symptoms become progressively worse, the patient should be advised to contact a primary care provider. In addition, if so-called alarm signs or symptoms are present, including blood in the stool or severe anal pain, or if symptoms persist beyond 7 days of self-treatment, the patient should be counseled to seek immediate medical attention.¹¹ If symptoms resolve, the patient should be encouraged to maintain a well-balanced diet, proper personal hygiene, and good bowel habits to avoid recurrence of symptoms.^{11,14,15,17}

Patient Education for Anorectal Disorders

The objectives of self-treatment are (1) to relieve specific signs and symptoms and (2) to prevent complications leading to serious problems. The primary goal of treatment is to prevent straining during defecation. For most patients, carefully following product instructions and the self-care measures listed here will help ensure relief of symptoms.

Nondrug Measures

- Maintain hydration and a healthy diet. If you are experiencing hard stools, straining, or constipation, increase the amount of fiber and fluids in the diet to reduce or prevent straining during bowel movements (see [Chapter 15](#)).
- Avoid medications that cause constipation, if possible (see [Chapter 15](#)).
- Clean anorectal area after each bowel movement with moistened,

unscented, white toilet tissue or wipe.

- Use a sitz bath, or soak in a bathtub 2–4 times a day, which may help relieve mild anal itching, burning, irritation, and discomfort. Avoid the use of soaps, salts, and oils.

Nonprescription Medications

- Select products containing only the ingredients needed to relieve specific anorectal symptoms.
- See [Table 17–3](#) for guidelines for applying anorectal products.
- See [Table 17–4](#) for recommended dosages of these products.
- Use only selected vasoconstrictors (ephedrine and phenylephrine), protectants (not glycerin), and astringents (calamine and zinc oxide) intrarectally.
- *If the patient is pregnant:* Use only products approved for external use. If internal use is required, any of the protectant class of drugs, with the exception of glycerin, may be used.
- *If the patient has a history of cardiovascular disease, diabetes, hyperthyroidism, hypertension, depression, or difficulty urinating because of prostate problems:* Avoid topical products that contain vasoconstrictors.
- *If the patient is taking medications for hypertension or depression:* Avoid using any anorectal product containing vasoconstrictors without first consulting your primary care provider.
- Self-monitor for nervousness, tremor, sleeplessness, nausea, and possible loss of appetite with use of an anorectal product containing ephedrine sulfate or phenylephrine.
- Expect a reduction or relief of symptoms within a few days of initiation of self-treatment.
- To support personal preferences, determine if a choice among an ointment, a cream, or a suppository is possible, or if generic products are available.

When to Seek Medical Attention

- Stop using the anorectal product and contact a primary care provider as soon as possible if insertion of a product into the

anorectal area causes pain.

- Contact a primary care provider if symptoms worsen, if new symptoms (e.g., bleeding) develop, or if symptoms do not resolve after 7 days of self-treatment.
- Discontinue using product and contact a primary care provider at the first occurrence of adverse effects (e.g., a new rash or increased itching, redness, burning, or swelling in the anorectal area).
- Discontinue product and contact a primary care provider immediately if allergic or hypersensitivity reactions to the anorectal product develop.

Key Points for Anorectal Disorders

- Self-treatment for anorectal disorders should be restricted to management of minor symptoms such as burning, itching, discomfort, swelling, and irritation.
- Immediate referral to a primary care provider is warranted when symptoms include anorectal seepage, bleeding, thrombosis, severe pain, fever, or a change in bowel patterns.
- The patient should be advised to seek medical attention if anorectal symptoms worsen or do not lessen after 7 days of self-treatment.
- Pregnant and breastfeeding women should be counseled to use only products for external use (except for protectants that do not contain glycerin, which can be used internally).
- Parents and caregivers of children younger than 12 years with anorectal symptoms need to seek further medical evaluation from their primary care provider.
- In selecting an anorectal product for self-treatment, opting for a preparation containing the fewest number of ingredients

necessary to treat specific symptoms will minimize the risk of undesirable effects.

- Patient education should include instruction in the proper use or application of specific anorectal products ([Table 17-3](#)).
- Counseling should identify effective nondrug management strategies (e.g., dietary measures, perianal hygiene) (see the box “Patient Education for Anorectal Disorders”).
- Medications with a vasoconstrictor effect should be avoided in patients who have conditions such as diabetes, hypertension, cardiac disease, thyroid disease, and enlarged prostate, or who are using antidepressants, to avoid the possibility of systemic adverse effects.
- Awareness of the advantages and disadvantages of various anorectal dosage forms will promote selection of the best product for the anorectal symptoms.

Chapter 18: Pinworm Infection

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Editor's Note: This chapter is based on the 19th edition chapter of the same title, written by Jeffrey A. Goad and Edith Mirzaian.

Enterobius vermicularis, commonly referred to as pinworm, seatworm, or threadworm, is an intestinal roundworm (nematode) and the primary agent that causes human pinworm infection (enterobiasis, also known as oxyuriasis).^{1,2} This chapter focuses on the detection and management of pinworm infection, as it is the most common intestinal helminthic (parasitic worm) infestation in the United States and the only helminthic infection for which a nonprescription medication has been approved for treatment by the U.S. Food and Drug Administration (FDA).^{1,3} Pinworm infection is common worldwide; in the United States, it is found with a high prevalence (estimated 40 million persons infected) in child care settings and urban areas owing to its highly contagious nature.^{2,4–8} Nearly 50% of all *E. vermicularis* cases occur among persons who are institutionalized (e.g., in child care facilities or in hospitals) and among household members.^{2,9,10} Enterobiasis is seen at all socioeconomic levels and, in contrast with other helminthic infections, has no apparent predilection for any particular racial or cultural group.¹ Although pinworms are a nuisance, the pinworm infection presents little risk to the infected person or to the public.

Pathophysiology of Pinworm Infection

Humans are the only known hosts of *E. vermicularis*.² Unlike with most other helminthic infections, pinworms do not live in the soil or water and are not transmitted through contact with animal feces. However, animal fur of household dogs and cats may be a carrier of infective eggs.¹⁰ The most common pinworm transmission route is through the fecal–oral ingestion of eggs from direct anus-to-mouth transfer by fingers or indirect egg transfer from the perianal region through fomites (e.g., clothes, bedding, bathroom fixtures). Reinfection may occur readily because eggs often are found under fingernails of infected children who have scratched the anal area. Finger sucking also may be a source of infection, particularly in children with

recurring symptoms.¹⁰ Nail biting and nose picking have not been associated with the initial infection; however, they certainly can contribute to reinfection.¹¹ Owing to their small size, pinworm eggs sometimes can become airborne in dust and reach the intestinal tract through the nose with respiration.^{2,4} Eggs can remain viable outside the intestinal tract for up to 20 days and can spread during that time within a household, school, or other micro-community, particularly under humid conditions.¹

After infective eggs are ingested, they may hatch and release larvae in the small intestine. The time lapse between ingestion of the eggs to oviposition (deposition of eggs) by adult females is approximately 1–2 months.⁴ After this period, the adult pinworm emerges as a small, white, thread-like worm with a pin-shaped, pointed tail from which the name is derived (see [Color Plates](#), photograph 5A); its lifespan is approximately 2 months.^{1,9} Adult male and female worms inhabit the ileocecum but seldom cause damage to the intestinal wall. The mature female, approximately 8–13 mm in length, usually stores approximately 11,000 eggs in her body (see [Color Plates](#), photograph 5B). After her nocturnal migration down the colon and through the anus, she deposits her sticky eggs in the perianal region and dies shortly afterward. The smaller males (2–5 mm) live about 2 weeks and do not migrate. If the eggs are not washed off, they hatch within a few hours, and larvae may return to the large intestine through anal retroinfection. Within 2–6 weeks of egg ingestion, larvae are released and mature into gravid females, thus continuing the cycle indefinitely unless appropriate behavioral and pharmacotherapeutic interventions are instituted.⁹ Extraintestinal infestations are rare but pinworms may mistakenly crawl into the genitourinary tract in females.⁴ Genitourinary pinworm infections are harder to treat because of the low systemic absorption of antiparasitic agents.¹

Clinical Presentation of Pinworm Infection

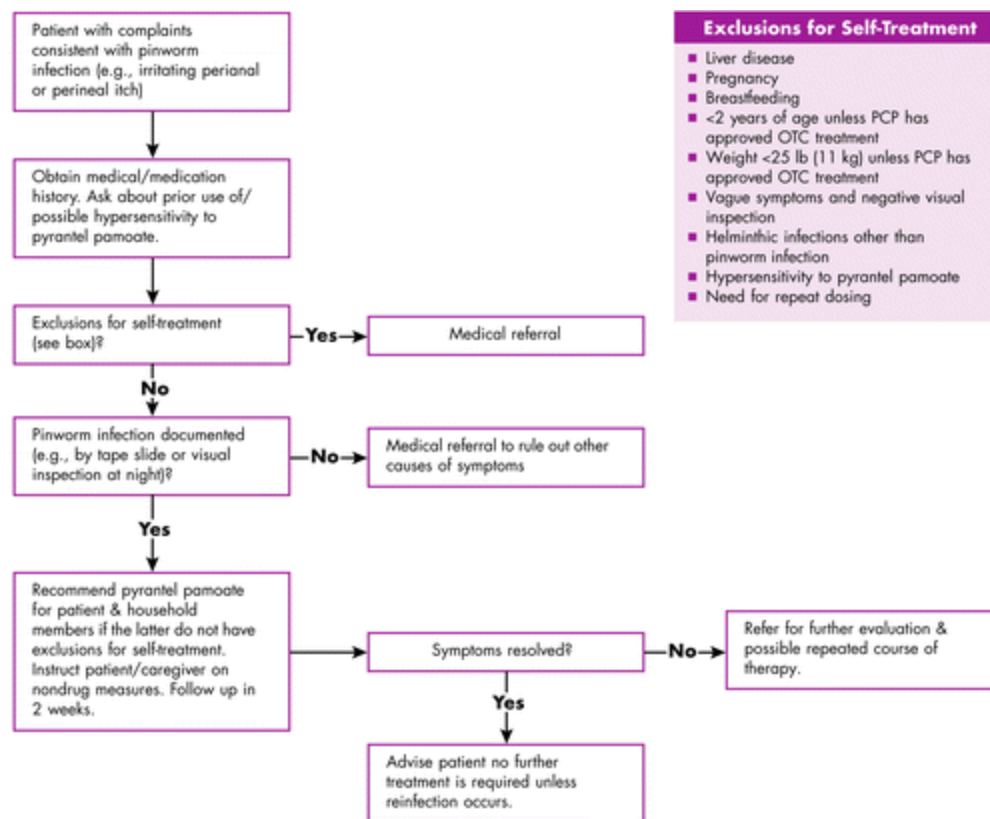
Patients with minor pinworm infections often are asymptomatic. Nocturnal perianal or perineal pruritus is the most common symptom.⁴ Perianal itching occurs predominantly at night and is caused by an inflammatory reaction to the presence of adult worms and eggs on the perianal skin.⁸ Major infections may produce clinical manifestations ranging from abdominal pain, insomnia, and restlessness to anorexia, diarrhea, and intractable localized itching.^{10,11} Patients with severe symptoms or extraintestinal infestation should be referred

for further evaluation. Before recommending treatment or medical referral, the pharmacist should ask appropriate assessment questions to rule out diaper dermatitis (see [Chapter 36](#)) in children, as well as constipation (see [Chapter 15](#)) and hemorrhoids (see [Chapter 17](#)) in older patients, because these conditions also can cause inflammation in the anorectal region, leading to itching and discomfort.

In addition to physical signs and symptoms, psychological trauma (previously referred to as *pinworm neurosis*) to patients and parents can occur when worms are found near the affected child's anus. Patients and parents need to be assured that pinworm infections are common and curable, and no social stigma should be attached to their occurrence.¹¹

Scratching to relieve itching from pinworm infection also may lead to secondary bacterial infection of the perianal and perineal regions.¹ Helminthic infections in the genital tract may progress to endometritis, salpingitis, tubo-ovarian abscess, pelvic inflammatory disease, vulvovaginitis, and possibly infertility.^{1,12,13} Pinworms also may migrate into the peritoneal cavity, where they may form granulomas. Rarely, pinworms may cause appendicitis in children.¹⁴

Algorithm: Pinworm Infection



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Figure 18–1 Self-care for pinworm infection. Key: OTC = Over-the-counter; PCP = primary care provider.

Treatment of Pinworm Infection

Treatment Goals

The goals of self-treatment are (1) to eradicate the pinworm infection, thereby relieving symptoms, (2) to prevent reinfection, and (3) to prevent transmission to other persons.

General Treatment Approach

The management of pinworm infection to include prevention of reinfection begins with treatment with pyrantel pamoate for the patient and for every household member. Strict hygiene (e.g., washing linens, disinfecting toilet

seats) is an integral part of the treatment plan. [Figure 18–1](#) outlines self-care for this infection and lists exclusions for self-treatment.

Nonpharmacologic Therapy

Once pinworm infection is suspected, the patient or caregiver should follow the nondrug measures in [Table 18–1](#) to minimize the occurrence of family and household infections and reinfections. Children usually can return to school after the first dose of an appropriate antihelminthic agent and after their fingernails are cut and cleaned. Health care providers are in an ideal position to inform patients and caregivers of behaviors that may increase their risk of helminthic infections.

Table 18–1 Nondrug and Preventive Measures for Pinworm Infection

- Educate patients in personal hygiene, particularly regarding the need to wash hands before eating or preparing food and after using the toilet. Encourage keeping fingernails short to prevent harboring of eggs and autoinoculation (hand-to-mouth reinfection); discourage biting nails and scratching in the anorectal region.
- Eggs are destroyed by sunlight and ultraviolet light, so ensure that blinds or curtains are open in the affected room(s) to enhance cleansing the environment.
- Wash bed linens, underwear, bedclothes, and towels of the infected person and entire household in hot water daily during treatment. Pinworm eggs are killed by exposure to temperatures of 131°F (55°C) for a few seconds, so the “hot” cycle should be used for washing and drying.
- Bathe daily in the morning; showers are preferred over baths.
- Change underwear, nightclothes, and bed sheets daily for several days after treatment.
- Clean and vacuum (do not sweep) the house daily for several days after treatment. Wet mopping before or instead of vacuuming may limit spread of pinworm eggs into the air.

Source: Heymann D. *Control of Communicable Diseases Manual*. 19th ed. Washington, DC: American Public Health Association; 2008.

Pharmacologic Therapy

Pyrantel Pamoate

Pyrantel pamoate is the only FDA-approved nonprescription medication for treatment of pinworm infection. Pyrantel pamoate was first used in veterinary

practice as a broad-spectrum drug for eradication of pinworms, roundworms, and hookworms. Pyrantel pamoate has a cure rate of 90%–100% when used for treatment of enterobiasis.¹⁵ The drug's less than perfect expected efficacy may be a result of a variable effect on pinworm eggs and larvae or reflect the viability of this helminth's eggs (up to 20 days), which may lead to reinfection.

Pyrantel pamoate is a depolarizing neuromuscular agent that stimulates the release of acetylcholine and inhibits cholinesterase, thereby paralyzing adult worms in the gastrointestinal (GI) tract. The paralyzed adult worms loosen their hold on the intestinal wall and are subsequently passed out in the stool. The drug is poorly absorbed, with 50% excreted unchanged in the feces and approximately 7% excreted in the urine as unchanged drug and metabolite (*N*-methyl-1,3-propanediamine).¹⁵

Pyrantel pamoate is indicated for nonprescription use in patients aged 2 years and up who weigh at least 25 lb (11 kg). The weight-based dosage chart on the package label, which is based on 11 mg/kg of pyrantel base, should be followed, up to the maximum dose of 1 g to be given as a single oral dose. Product labeling includes a schedule of recommended dosages based on a range of body weights. Dosing can be repeated in 2 weeks if symptoms do not resolve, because reinfection can occur; however, the repeat dose should be administered only after consultation with a primary care provider. Pyrantel pamoate may be taken at any time of day without regard to meals, and it may be taken or mixed with milk or fruit juice.¹⁵ Liquid formulations (containing the equivalent of 50 mg/mL of pyrantel base) must be shaken before the dose is measured with the measuring device enclosed with the product packaging.

Adverse effects of pyrantel pamoate usually are mild, infrequent, and transient. The most common adverse effects involve the GI tract: nausea, vomiting, gastralgia, abdominal cramps, diarrhea, and anorexia.¹⁶ These adverse effects may be related to expulsion of helminths from the GI tract. Less common adverse effects include headache, dizziness, drowsiness, insomnia, rash, fever, and weakness. In very rare circumstances, transient increases in aspartate aminotransferase (AST) have been reported. Patients who experience severe or persistent adverse effects after taking this medication should be referred for further medical evaluation. Patients who do not respond to pyrantel pamoate should be advised to see their primary care provider, and the use of prescription medications (e.g., albendazole, mebendazole) should be considered.

Product Selection Guidelines

Pyrantel pamoate is a safe and effective agent for treatment for pinworms. The medications listed in [Table 18–2](#) are comparatively priced and generally less expensive overall than prescription antihelminthics. Pyrantel pamoate is contraindicated in patients with hypersensitivity to this medication. Patients with preexisting liver dysfunction, severe malnutrition, or anemia should not use pyrantel pamoate without first consulting a primary care provider. Use of pyrantel pamoate in pregnancy and during breastfeeding should be limited to situations in which the potential benefit justifies potential risk to the child and then is allowed only under the direction of a primary care provider. Finally, pyrantel pamoate should not be used on a self-care basis in patients younger than 2 years of age or those weighing less than 25 lb (11 kg).

Table 18–2 Selected Nonprescription Pyrantel Pamoate Products	
Trade Name ^a	Primary Ingredient
Reese’s Pinworm Medicine Liquid	Pyrantel pamoate 50 mg/mL (base) [banana flavored]
Reese’s Pinworm Medicine Family Pack	Pyrantel pamoate 50 mg/mL (base); contains two bottles (each containing 1 fluid ounce) to treat the entire family [banana flavored]

^a Various store brand and other generic formulations also are available.

Complementary Therapies

Numerous home remedies (e.g., applying a combination of garlic paste and petroleum jelly to the anus, ingesting coconut or castor oil) and complementary therapies (e.g., white willow bark, green tea, turmeric) have been used to treat pinworm infection. These remedies are not recommended, however, because evidence of their efficacy and safety is lacking to support their use to treat pinworm infections.

Assessment of Pinworm Infection: A Case-

Based Approach

Before recommending treatment, the health care provider should explain how to confirm a pinworm infection by any of the following methods: (1) nighttime perianal or perineal itching in a child, (2) visual inspection of the perianal or perineal area for the adult worm, or (3) a cellophane tape or an adhesive paddle test. Adult pinworms and eggs are seldom found in the feces, so looking for worms in the stool is not a reliable way to diagnose enterobiasis.¹⁷ When symptoms of pinworms (e.g., nocturnal perianal, perineal itching) are present in children, nonprescription therapy may be initiated. With more vague complaints such as sleep disturbances or GI symptoms, the patient should first be evaluated by a primary care provider before initiation of nonprescription therapy.

Asymptomatic disease is common in enterobiasis; therefore, a visual inspection may be necessary for confirmation. The parent should inspect the anal area during the night with a flashlight while the child is sleeping or in the very early morning before the child arises. White, thread-like, wriggling worms, about the size of a staple, may be seen; this finding confirms the infection and prompts initiation of treatment. Finally, if pinworms are suspected but symptoms are vague in nature or the visual inspection fails to show confirmatory evidence, obtaining a cellophane tape sample may be warranted. The parent should apply the sticky side of the tape to the perianal area (usually with a tongue depressor) and then place it sticky side down on a glass slide. Commercially available kits use a sticky paddle instead of tape to affix to a slide (see [Color Plates](#), photograph 5C). Samples should be taken over 3 consecutive days upon the child's awakening, which may increase the likelihood of detection to around 90%.¹¹ The samples should then be taken to an appropriate health care provider to submit for microscopic examination. If the test result is positive, treatment for pinworm infection should be initiated. Cases 18–1 and 18–2 illustrate the assessment of two different patients with symptoms of pinworm infection.

Case 18–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patients' symptoms, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	A woman presents to the pharmacy requesting assistance in selecting a nonprescription product. She reports that her daughter was diagnosed as having pinworms by her pediatrician, who recommended a nonprescription medication for treatment. The mother says her daughter has been complaining about perianal itching that gets much worse at night. The mother and her husband have no current symptoms. The mother asks for a liquid or chewable formulation since her daughter has a hard time swallowing tablets or capsules.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patients' symptom(s)	No precipitating factors
c. Description of the patients' efforts to relieve the symptoms	The parents gave their daughter liquid Benadryl for the itching, with no relief.
d. Patients' identity	The family consists of daughter Jenny, mother Theresa North, and father Robert North.
e. Patients' age, gender, height, and weight	<i>Daughter:</i> 6 years, female, 3 ft 6 in., 40 lb (18 kg)
	<i>Mother:</i> 36 years, female, 5 ft 6 in., 143 lb (65 kg)
	<i>Father:</i> 38 years, male, 5 ft 11 in., 190 lb (86 kg)
f. Patients' occupations	Jenny is in first grade in elementary school. Mrs. North is an attorney, and Mr. North is a mechanical engineer.
g. Patients' dietary	All family members report normal diet and appetite.

Relevant Evaluation Criteria	Scenario/Model Outcome
habits	
h. Patients' sleep habits	<i>Daughter:</i> frequent awakenings at night caused by perianal itching; <i>parents:</i> normal sleep habits
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	<i>Daughter:</i> daily children's chewable multivitamin; <i>mother:</i> daily multivitamin; <i>father:</i> fish oil capsule daily, baby aspirin
j. Allergies	<i>Daughter:</i> amoxicillin allergy (rash); <i>mother:</i> NKA; <i>father:</i> NKA
k. History of other adverse reactions to medications	None
l. Other (describe) -----	n/a
Assess	
2. Differentiate patients' signs/symptoms, and correctly identify the patient's primary problem(s).	Jenny is experiencing perianal itching from a pinworm infection, which results in restless sleep at night.
3. Identify exclusions for self-treatment (Figure 18-1).	Patients should be excluded from eligibility for self-treatment if they (1) are allergic to the nonprescription product, (2) are younger than 2 years of age (unless treatment is approved by a primary care provider), (3) weigh less than 25 lb (11 kg) (unless treatment is approved by a primary care provider), (4) have liver disease, (5) are pregnant, (6) are breastfeeding, (7) have vague symptoms and no evidence of infection on visual inspection, (8) have severe symptoms, (9) have anemia, (10) have malnutrition, or (11) have symptoms outside of the perineal region.
	Jenny does not have any exclusions for self-treatment, and neither do Mr. and Mrs. North, who also should be treated because pinworm infection can spread within a household.

Relevant Evaluation Criteria	Scenario/Model Outcome
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patients or caregiver.	Options include (1) Recommend an appropriate nonprescription product (i.e., pyrantel pamoate) at the proper dose for each member of the family, along with nondrug measures. (2) Recommend that the parents see a primary care provider for a prescription medication while Jenny receives nonprescription pyrantel pamoate. (3) Counsel only on environmental control measures and nondrug strategies for all family members. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patients' problem, taking into account patient preferences.	Nonprescription treatment with pyrantel pamoate is appropriate for all three patients. The child is not comfortable swallowing tablets or caplets, but she can take chewable tablets or a liquid formulation. Pyrantel pamoate liquid formulation is therefore an appropriate option.
6. Describe the recommended therapeutic approach to the patients or caregiver.	"Several medications are effective in the treatment of pinworms. Pyrantel pamoate is available without a prescription. Because a family member was recently diagnosed with pinworm infection and the primary care provider instructed that the patient be treated with a nonprescription medication, all family members should also be treated, since infection can spread within the household. Therefore, pyrantel pamoate is a reasonable option."
7. Explain to the patients or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Pinworm infection is not life-threatening. However, if the infection is untreated, your daughter may reinfect herself or infect other family members. She also may experience some complications of infection if she is not treated. Pyrantel pamoate is a reasonable treatment option because it is available without a prescription. Pyrantel pamoate is available as an oral suspension, which offers flexible dosing based on weight for multiple family members."

Relevant Evaluation Criteria	Scenario/Model Outcome
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patients or caregiver.	
a. Appropriate dose and frequency of administration	Follow the dosage chart found on the medication package label to take a single weight-based dose; do not exceed more than 1 g of pyrantel pamoate base. Use the enclosed measuring device for any liquid formulations. • Jenny weighs 40 lb (18 kg), so the dose is 1 teaspoonful according to the medication package dosage chart. • Mrs. North weighs 143 lb (65 kg), so the dose is 3 teaspoonfuls according to the medication package dosing chart. • Mr. North weighs 190 lb (86 kg), so the dose is 4 teaspoonfuls according to the medication package dosing chart. [Note: It is important to reinforce to the parents that pinworms are very common and rarely cause serious problems, but that the infection will continue and potentially spread to others if it is not properly treated.]
b. Maximum number of days the therapy should be employed	“Treatment usually consists of a single dose. If symptoms persist after 2 weeks, contact your primary care provider for evaluation and, if needed, a recommendation for a second dose.”
c. Product administration procedures	“Pyrantel pamoate may be taken at any time of day without regard to meals. It may be mixed with milk or fruit juice. If using the oral suspension, shake well before administering.”
d. Expected time to onset of relief	“Relief of symptoms may take several days. A repeat dose should not be administered until 2 weeks have elapsed and should be administered only if recommended by your primary care provider.”

Relevant Evaluation Criteria	Scenario/Model Outcome
e. Degree of relief that can be reasonably expected	Perianal itching should decrease after several days, with complete pinworm eradication after at least 2 weeks.
f. Most common adverse effects	Adverse effects are usually mild and may consist of nausea, vomiting, loss of appetite, diarrhea, or abdominal cramps.
g. Adverse effects that warrant medical intervention should they occur	Severe or persistent abdominal symptoms require medical attention.
h. Patient options in the event that condition worsens or persists	“Contact the appropriate health care provider if a family member’s condition worsens, or if, after taking the medication, a family member experiences any severe adverse effects, such as severe or persistent abdominal symptoms.”
i. Product storage requirements	Store at room temperature away from direct light with container sealed tightly.
j. Specific nondrug measures	See Table 18-1 .
Solicit follow-up questions from the patients or caregiver.	“Should my daughter receive a prescription medication instead because she has an active infection?”
Answer the patients’ or caregiver’s questions.	“Both the prescription and nonprescription medications are equally effective in treating pinworms. You can use either the prescription medication or the nonprescription pyrantel pamoate, depending on your preferences (such as cost).”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	You can call the parents in 1–2 weeks to assess the child’s response to the medication. If symptoms have resolved, reinforce the importance of hygienic measures. If symptoms persist, another single dose of pyrantel pamoate can be administered, but only after reevaluation by the child’s pediatrician or the family’s regular health care provider.

Key: n/a = Not applicable; NKA = no known allergies.

Case 18–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	A woman comes to the pharmacy requesting assistance in choosing a product to help with diarrhea. She says she has had diarrhea, itching around the perianal region, and generalized abdominal pain for about 4 days. The itching, which began roughly 1 week before the diarrhea started, tends to be worse at night. She also tells you that her grandchildren, whom she visited in another state about 2 weeks ago, had similar symptoms of itching as well and that her daughter was going to take them to see their pediatrician.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	No precipitating factors
c. Description of the patient's efforts to relieve the symptoms	She tried bismuth subsalicylate for 3 days without much relief. She took 3 doses of loperamide, which helped with the diarrhea but did not stop the itching. She tried applying hemorrhoidal ointment and hydrocortisone ointment to the region to help with the itching, with limited relief.
d. Patient's identity	Letty Whitaker
e. Patient's age, gender, height, and weight	61 years, female, 5 ft 4 in., 132 lb (60 kg)
f. Patient's occupation	Dance instructor
g. Patient's dietary habits	Normal diet, high in fruits, vegetables, and whole grains

Relevant Evaluation Criteria	Scenario/Model Outcome
h. Patient's sleep habits	Frequent awakenings at night caused by perineal itching
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Daily multivitamin; occasional ibuprofen or acetaminophen for pain
j. Allergies	NKA
k. History of other adverse reactions to medications	None
l. Other (describe) -----	n/a
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Ms. Whitaker's symptoms, such as perianal itching at night, are consistent with pinworm infection, but diarrhea and abdominal pain are unusual symptoms in this setting and warrant evaluation by an appropriate health care provider. A tape test or a slide test should be done to confirm pinworm infection.
3. Identify exclusions for self-treatment (Figure 18-1).	Eligibility for self-treatment is ruled out by any of the following: (1) allergy to the nonprescription product, (2) age younger than 2 years (unless treatment is approved by a primary care provider), (3) body weight less than 25 lb (11 kg) (unless treatment is approved by a primary care provider), (4) liver disease, (5) pregnancy, (6) breastfeeding, (7) vague symptoms with no findings on visual inspection, (8) severe symptoms, (9) anemia, (10) malnutrition, or (11) symptoms outside of the perineal region.
	Ms. Whitaker is excluded from self-treatment because she has vague symptoms and negative visual inspection.
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care	Options include (1) Recommend an appropriate nonprescription product at the proper dose, along with nondrug therapies.

Relevant Evaluation Criteria	Scenario/Model Outcome
provider is required, and share this information with the patient or caregiver.	(2) Refer Ms. Whitaker to an appropriate health care provider for further evaluation, diagnosis, and recommended treatment. (3) Counsel Ms. Whitaker on environmental control measures and nondrug strategies only. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Medical evaluation by an appropriate health care provider is warranted because of the perineal and gastrointestinal symptoms, which may necessitate prescription treatment.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"You should see your primary care provider for further evaluation of your symptoms, appropriate diagnosis, and recommended treatment."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Because you do not have a documented pinworm infection and because you have other symptoms that may be complications of other conditions, self-treatment is not appropriate. Your symptoms may be consistent with pinworm infection, but other possibilities need to be ruled out."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	"Self-treatment is not appropriate, but you should start environmental control and nondrug measures [see Table 18–1] and seek medical care."

Relevant Evaluation Criteria	Scenario/Model Outcome
Solicit follow-up questions from the patient or caregiver.	(1) "Are there any complications associated with pinworms?"
	(2) "How are pinworms normally treated?"
Answer the patient's or caregiver's questions.	(1) "If untreated, pinworm infection could lead to secondary bacterial infections in the perianal and perineal regions. Pinworm infections also can lead to pelvic inflammatory disease, endometritis, and urinary tract infections. In addition, other possible symptoms associated with pinworm infection include insomnia, restlessness, and anorexia."
	(2) "Patients with pinworm infection may be treated with a single dose of nonprescription (pyrantel pamoate) or prescription (albendazole, mebendazole) medications. Along with medications, patients also must follow specific nondrug measures to prevent reinfection."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Ask Ms. Whitaker to call you in 1 week, or initiate a follow-up call to ensure she was evaluated by an appropriate health care provider and whether her symptoms are resolving.

Key: NKA = No known allergies.

Patient Counseling for Pinworm Infection

Once the decision to treat the pinworm infection with pyrantel pamoate is made, the package insert material should be reviewed with the patient or caregiver. The insert explains the pinworm life cycle, symptoms of pinworm infection, and methods of transmitting the infection. Doses should be calculated for the patient and all family members, and the need to treat the whole family should be emphasized. The patient or caregiver will need to implement strict hygienic measures to prevent reinfection or transmission of the infection to other family members ([Table 18–1](#)). In addition, it should be

explained that the adverse effects of pyrantel pamoate usually are mild and infrequent, but that medical referral may be necessary if more severe or persistent effects occur. Patients and caregivers should be advised that symptoms should resolve within 2 weeks of treatment. They should be further advised that persistence or worsening of symptoms that include systemic manifestations (e.g., abdominal discomfort, insomnia, nervousness) warrants further medical evaluation. The box “Patient Education for Pinworm Infection” lists specific information to provide in patient counseling.

Evaluation of Patient Outcomes for Pinworm Infection

Patients or caregivers should be instructed to contact their primary care provider if anal itching persists beyond 2 weeks, if the itching recurs, or if new symptoms develop. Because of pyrantel pamoate’s variable cure rate, a second dose may be required. It should be given 2 weeks after the first dose and only with the recommendation of a primary care provider. In addition, the importance of implementation of and adherence to hygienic measures should be emphasized to patients or caregivers. Following these measures is crucial for preventing reinfection.

Patient Education for Pinworm Infection

The objectives of self-treatment are (1) to eradicate pinworms in the infected patient, (2) to prevent reinfection, and (3) to prevent transmission of the infection to others. For most patients, carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

Nondrug Measures

- See [Table 18–1](#) for nondrug/preventive measures.

Nonprescription Medications

- Read package insert for pyrantel pamoate information carefully; this information is provided to help prevent reinfection or transmission of the infection.
- Consult a primary care provider before giving the medication to a person with liver disease, severe malnutrition, or anemia; a child who is younger than 2 years of age or weighs less than 25 lb (11 kg); a woman who is pregnant or breastfeeding; or someone who has vague or rare symptoms and no evidence of infection on visual inspection.
- Treat all household members to ensure elimination of the infection. Medical referral may be necessary if any household member meets criteria for exclusion for self-treatment (e.g., malnutrition, pregnancy, liver disease, anemia, age younger than 2 years).
- Take only 1 dose as shown on the dosage chart included with the product. For adults and children older than 2 years, oral dosing is based on 11 mg/kg of pyrantel base. The maximum dose is 1 g.
- Shake the liquid formulation well and use the measuring device enclosed within packaging to ensure an accurate dose.
- If desired, pyrantel pamoate may be taken with food, milk, or fruit juices or on an empty stomach, at any time of day. The liquid formulation may be mixed with milk or fruit juice.

When to Seek Medical Attention

Seek medical attention if you experience any of the following:

- Abdominal cramps, nausea, vomiting, anorexia, rash, diarrhea, headache, drowsiness, or dizziness occurs or persists after you take the medication.
- Symptoms of the pinworm infection that persist beyond 2 weeks after the initial dose of pyrantel pamoate. A second dose of pyrantel pamoate can be given if symptoms are present beyond 2 weeks, but only if recommended by a primary care provider.
- Rare symptoms and signs such as vaginal itching or bleeding, pain upon urination, urinary tract infection, and hives occur.

Key Points for Pinworm Infection

- Pinworm infections are common in the United States and rarely cause significant morbidity.
- Health care providers should be familiar with common helminthic infections, their symptoms, and their treatment.
- A medical referral is necessary when helminths other than pinworms are suspected.
- Although pyrantel pamoate may be used in treating other helminthic infections, only patients with pinworm infection should be evaluated for self-treatment with this nonprescription agent.
- Health care providers can aid patients and caregivers in self-diagnosis, counseling, and self-treatment with nonprescription medication for pinworm infection.

Chapter 19: Nausea and Vomiting

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Nausea, a subjective feeling of the need to vomit, and *vomiting*, a forceful expulsion of the contents of the gastrointestinal (GI) tract, also called emesis, can occur in both adults and children in association with a variety of circumstances and medical disorders. Common self-care disorders that involve nausea and vomiting (N/V) are motion sickness, “morning sickness” in pregnancy (nausea and vomiting of pregnancy [NVP]), acute viral gastroenteritis, and “upset stomach” (GI distress related to overeating or indigestion). Nonprescription antiemetics can be used to prevent or treat N/V associated with these disorders. Other causes of nausea are included in those listed in [Table 19–1](#). Nausea accounts for 324,000 emergency department visits for women aged 65 years and older, or 1.4% of all visits.¹ Vomiting accounts for 1.9% of all emergency department visits in the United States. Each year, nearly 2.8 million people, mostly children younger than 15 years, visit a hospital emergency department for vomiting.¹ Accurate data on the epidemiology of N/V are not available, because nausea as well as vomiting may occur in various medical disorders, and many affected persons do not report these disturbances to a health care provider.

Table 19–1 Primary Causes of Nausea and Vomiting

GI Tract Disorders^a	CNS Disorders	Other Disorders
Mechanical Obstruction GI obstruction (e.g., PUD, gastric carcinoma, pancreatic disease); small intestine obstruction Motility Disorders Gastroparesis (e.g., diabetes, drug-induced, postviral); chronic intestinal pseudo-obstruction; IBS; anorexia nervosa; idiopathic gastric stasis Peritoneal Irritation Appendicitis; bacterial peritonitis; pancreatitis Infections Viral gastroenteritis ^b (e.g., norovirus, rotavirus); food poisoning (e.g., bacterial	Vestibular Disorders Labyrinthitis; Ménière syndrome; motion sickness ^a Increased Intracranial Pressure CNS tumor; subdural or subarachnoid hemorrhage; pseudotumor cerebri Infections Meningitis; encephalitis Psychogenic Anticipatory vomiting; bulimia; psychiatric	Cardiac disease (e.g., MI, HF); urologic disease (e.g., stones, pyelonephritis); overeating ^a Diabetes (e.g., DKA); renal disease (e.g., uremia); adrenocortical crisis (e.g., Addison disease); pregnancy ^a Chronic cannabis use (e.g., CHS)

GI Tract Disorders ^a	CNS Disorders	Other Disorders
toxins from <i>Bacillus cereus</i> , <i>Staphylococcus aureus</i> , <i>Clostridium perfringens</i>); hepatitis A or B; acute systemic infections Topical GI Irritants Alcohol; NSAIDs; antibiotics, iron	disorders (anxiety) Other CNS Disorders Migraine headache Irritation of CTZ (medication-induced) Chemotherapy; opiates; theophylline or digoxin toxicity; antibiotics; radiation therapy; drug withdrawal (e.g., opiates, BDZs)	

^a Mediated by visceral afferent nerves.

^b Self-treatable or preventable disorders.

Key: BDZ = Benzodiazepine; CHS = cannabinoid hyperemesis syndrome; CNS = central nervous system; CTZ = chemotrigger receptor zone; DKA = diabetic ketoacidosis; GI = gastrointestinal; HF = heart failure; IBS = irritable bowel syndrome; MI = myocardial infarction; NSAIDs = nonsteroidal anti-inflammatory drugs; PUD = peptic ulcer disease.

Source: Reference 7.

Motion sickness rarely occurs in children younger than 2 years. An apparent gender predilection has been noted, with an increased susceptibility to motion sickness reported in females, as well as in children 2–15 years of age.² It is reported that NVP affects 70%–80% of pregnant women. Typically these symptoms occur during pregnancy between weeks 9 and 16, but they may begin as early as 2 weeks. They generally resolve by 22 weeks but may extend for the entire pregnancy in up to 10% of women.³ A severe form of pregnancy-related vomiting, *hyperemesis gravidarum*, occurs in less than 2%; however, it is the most common reason for hospitalization in the first half of pregnancy.³ Hyperemesis gravidarum may lead to maternal morbidity and adverse birth outcomes.³

Viral gastroenteritis is an inflammation of the stomach and small intestines that commonly manifests with acute vomiting and diarrhea.⁴ Often caused by

rotavirus or norovirus, this illness may affect any age group and usually is self-limiting, but pediatric patients may experience serious consequences from associated dehydration.⁴ Routine vaccination in infants can prevent rotavirus infection. Before availability of an effective vaccine, it was estimated that 3 million cases of rotavirus infection occurred each year, leading to more than 400,000 primary care visits.⁵ [Chapter 16](#) describes gastroenteritis in more detail.

The remaining self-care condition that involves N/V is indigestion or abdominal distention associated with overeating. An overview of treatment options for this condition is presented in this chapter. A more comprehensive discussion is provided in [Chapter 13](#).

Pathophysiology of Nausea and Vomiting

The pathophysiology of N/V is highly complex and involves the physiologic state, GI tract, central nervous system (CNS), and autonomic nervous system.⁶ The threshold at which a person can experience nausea is variable, potentially changing from moment to moment. Anxiety or anticipation can induce nausea (butterflies in the stomach). Stimuli arising from visceral (gut) or vestibular (inner ear) loci or in the chemoreceptor trigger zone (brain) can lead to nausea. Nauseogenic stimuli originating viscerally or in the chemoreceptor trigger zone typically are mediated by serotonin and dopamine. Vestibular stimuli related to the body's motion and position are mediated by histamine type 1 (H₁) receptors and acetylcholine.⁷ When the inner ear labyrinth apparatus detects a body position that conflicts with sensory inputs such as vision, motion sickness can occur. Vomiting, mediated largely by the autonomic nervous system, often is preceded by signs and symptoms of sweating, pallor, salivation, increased blood pressure and heart rate, and decreased gastrointestinal motility.⁷ Vomiting, or emesis, occurs on detection of emetic agents in the blood by chemosensitive receptors. A rise in vasopressin levels also has been shown to precede vomiting.⁷ The mechanism of NVP is less known and may be multifactorial, with genetic, endocrine, and gastrointestinal influences.³ In N/V related to overeating, gut distention and a decrease in GI motility may stimulate mechanoreceptors, leading to symptoms.⁶

Clinical Presentation of Nausea and Vomiting

Three different processes are recognized in N/V: (1) *nausea* (characterized by a person's subjective feeling of a need to vomit); (2) *retching* (involuntary rhythmic diaphragmatic and abdominal contractions prior to vomiting); and (3) *vomiting* (rapid, forceful expulsion of GI tract contents).⁸ Although most cases of N/V are self-limiting, the presence of certain signs and symptoms warrants medical referral. Possible acute complications of vomiting include dehydration, esophageal rupture manifested by blood in the vomitus, aspiration, malnutrition, electrolyte and/or acid–base abnormalities, diaphragmatic herniation, and Mallory–Weiss syndrome.⁹ Dehydration and electrolyte imbalances are the major concerns associated with vomiting. Signs and symptoms of dehydration include dry mouth, decreased skin turgor, excessive thirst, limited or cessation of urine output, dizziness, lightheadedness, fainting, and reduced blood pressure.^{9,10} These findings warrant medical referral for further evaluation.

In infants and small children, recurrent or protracted N/V (with accompanying diarrhea) may lead to marked dehydration and electrolyte imbalances; clinical manifestations of such disturbances must not be ignored. Parents should be educated to recognize signs and symptoms of dehydration, such as dry mucous membranes, decreased skin turgor, irritability, altered mental status, and weight loss ([Table 19–2](#)).¹⁰ Referral for further evaluation is indicated if the child has any exclusions for self-care management of N/V.

Table 19–2 Signs and Symptoms of Dehydration in Children

- Restlessness or irritability
- Rapid or deep breathing
- Tachycardia
- Dry mouth and tongue
- Sunken and/or dry eyes
- Sunken fontanelle
- Decreased urine output (dry diapers for several hours)
- Dark urine
- Thirst (drinks extremely eagerly)
- Absence of tears when crying
- Decreased skin turgor
- Prolonged capillary refill in the fingertip after release of a gentle squeeze

- Weight loss
 - Noticeable decrease in abdominal (“tummy”) size
 - Loose fit of clothing or diaper
 - <3% body weight loss, indicating minimal or no dehydration
 - 3%–9% body weight loss, indicating mild to moderate dehydration
 - >9% body weight loss, indicating severe dehydration

Source: Reference 9.

Treatment of Nausea and Vomiting

Treatment Goals

The goals of treating N/V are (1) to provide symptomatic relief, (2) to identify and correct the underlying cause, (3) to prevent and correct complications, and (4) to prevent future occurrences.

General Treatment Approach

Most acute cases of N/V are self-limiting and will resolve spontaneously. A careful evaluation is indicated to determine whether a patient is a candidate for self-treatment. The algorithms in [Figures 19–1](#) and [19–2](#) outline the self-treatment options and exclusions for self-care for N/V in adults and children,^{11–14} respectively. Severe cases of vomiting can result in dehydration or electrolyte imbalances, which may necessitate further evaluation or hospitalization. Treatment of N/V can involve pharmacologic prescription and nonprescription therapies, as well as nonpharmacologic options. Pharmacologic nonprescription options are limited and include antihistamines.

Nonpharmacologic Therapy

Because most cases of N/V are acute, nonpharmacologic treatment is directed primarily at correcting dehydration and electrolyte imbalances. Commercial oral rehydration solutions (ORSs) should be recommended to prevent these

complications. These products contain sodium, chloride, potassium, citrate, and a carbohydrate such as glucose or dextrose to restore loss of electrolytes and also restore loss of fluids. ORSs can be used for dehydration associated with vomiting or diarrhea.¹⁵ In cases of vomiting, absorption of fluids may be compromised by continuous emesis in some patients. Details on ORSs can be found in [Chapter 16](#). Sports drinks, such as Gatorade or Powerade, often do not contain the recommended balance of electrolytes. The preferred ratio of sugar to sodium is 3:1. Original-formula Gatorade contains a sugar-to-sodium ratio of 15:1. Dilution of sports drinks with water by the patient may be an option, but it is difficult to achieve accurate sugar-to-sodium ratios, and sports drinks often are available in multiple formulations. Too much sugar may draw water into the GI tract, facilitating further dehydration. Similarly, sodas, such as ginger ale or cola, and fruit juices, such as apple, also may contain too much sugar.^{16,17}

The typical dosing for ORSs varies according to the level of dehydration and the age and weight of the patient. For minimal dehydration, children weighing less than 10 kg should be given 60–120 mL of solution after each vomiting episode; children weighing 10 kg or more should be given 120–240 mL per episode. All children with mild to moderate dehydration should receive an ORS at a dosage of 50–100 mL/kg over 3–4 hours. Those with severe dehydration should be referred to emergency care centers for intravenous rehydration.¹⁸ Adults also should receive ORS therapy for rehydration, but the amount of replacement fluid needed generally can be gauged according to thirst. Replacing 30%–50% of the fluid loss in the first 24 hours is preferred.¹⁸

ORSs should be offered 10 minutes after the last episode of vomiting and provided in small increments. In general, 5 mL of an ORS may be given to children every 5 minutes, and 15 mL may be given to older children and adults every 5 minutes.¹⁸ Dosage forms such as Pedialyte Freezer Pops may allow the slow administration desirable with active vomiting.

For minimizing motion sickness, preventive measures can be found in [Table 19–3](#).

Table 19–3 Nonpharmacologic Measures to Prevent Motion Sickness

- Avoid reading during travel.
- Focus the line of vision fairly straight ahead (e.g., seat the patient in a position that allows vision out of the car window).

- Avoid excess food or alcohol before and during extended travel.
- Sit where motion is least experienced (e.g., front of the car; near the wings of an airplane; or midship [midway between bow and stern], preferably on deck).
- Avoid strong odors, particularly from food or tobacco smoke.
- Drive the vehicle if possible.

Source: Reference 2.

Pharmacologic Therapy

Selection of a nonprescription medication for N/V is largely determined by the potential cause. No specific nonprescription medications have been recommended for the treatment of viral gastroenteritis or food poisoning. Management options for these conditions are aimed at oral rehydration and are described under “Nonpharmacologic Therapy.”

Nausea Associated With Motion Sickness

Antihistamines are effective and generally safe and well tolerated for N/V related to motion sickness.² A detailed description of antihistamines can be found in [Chapter 11](#). Meclizine, dimenhydrinate, and diphenhydramine are U.S. Food and Drug Administration (FDA)-approved nonprescription agents for the prevention of nausea, vomiting, or dizziness associated with motion sickness.¹⁹ Second generation antihistamines are ineffective for treating motion sickness.² Doxylamine has been used for off-label treatment for nausea. [Table 19–4](#) lists age-specific dosages and maximum daily limits for these antiemetics.^{20,21} Through their anticholinergic effects, antihistamines may thicken bronchial secretions and should therefore be used with caution in patients with respiratory conditions such as asthma, chronic bronchitis, and emphysema. In addition, the mydriatic effects of antihistamines may exacerbate angle-closure glaucoma. The urinary retention effects of antihistamines also may worsen symptoms of benign prostatic hypertrophy. Other adverse effects of nonprescription antihistamines include dry mouth, confusion, dizziness, tremors, and constipation.²² Drowsiness also is a common adverse effect of antihistamines. Patients should avoid concomitant use of antihistamines with other CNS depressants, such as alcohol, hypnotics, and sedatives. This drowsiness, coupled with the potential for blurred vision, may impair the ability

to drive safely or operate heavy machinery. Meclizine may be less sedating and longer acting than dimenhydrinate.¹⁹ Meclizine also may be less sedating than doxylamine and diphenhydramine. Paradoxical stimulatory reactions such as insomnia, nervousness, and irritability may occur in some patients.

Table 19–4 Dosage Guidelines for Nonprescription Antiemetic Antihistamines^a

Agent	Dosage (maximum daily dosage)		
	Adults and Children ≥ 12 Years	Children 6 to < 12 Years	Children 2 to < 6 Years
Cyclizine	50 mg 30 minutes before travel, then 50 mg every 4–6 hours (200 mg)	25 mg every 6–8 hours (75 mg)	Not recommended
Dimenhydrinate	50–100 mg every 4–6 hours (400 mg)	25–50 mg every 6–8 hours (150 mg)	12.5–25 mg every 6–8 hours (75 mg)
Diphenhydramine	25–50 mg every 6–8 hours (300 mg)	12.5–25 mg every 6–8 hours (150 mg)	Not recommended
Meclizine	25–50 mg 1 hour before travel (50 mg)	Not recommended	Not recommended
Doxylamine ^b	In pregnancy, 10–12.5 mg with or without pyridoxine every 8 hours	Not recommended	Not recommended

^a Take antihistamines at least 30–60 minutes before travel; then take continuously for the duration of travel.

^b Off-label use for nausea and vomiting of pregnancy.

Source: References 2 and 19.

Nausea Associated With Food or Beverages

N/V may be associated with overindulgence in food or beverage or consumption of spoiled or other disagreeable foods, and it may manifest as heartburn, indigestion, and upset stomach. Antacids and histamine type 2 (H₂) receptor antagonists (H₂RAs) are approved for relief of symptoms associated

with acid indigestion and “sour stomach.” However, antacids have marginal efficacy for the treatment of N/V secondary to nonulcer dyspepsia. Patients with prolonged and predominant nausea and bloating should be referred for further evaluation, because such disturbances may be a sign of GI motility dysfunction, *H. pylori* infection, duodenal abnormalities, or other conditions that would require prescription treatments.^{23,24}

Bismuth subsalicylate (BSS) may be of some benefit for relief of nausea associated with consumption or nonulcer dyspepsia.²³ BSS is approved to treat various GI symptoms, including nausea, heartburn, and fullness. In-depth discussion of use of BSS can be found in [Chapters 13](#) and [16](#).

Phosphorated carbohydrate solution (PCS) also may be useful in combating nausea associated with food or beverage consumption. PCS is a mixture of dextrose (glucose), levulose (fructose), and phosphoric acid.²⁵ This hyperosmolar solution is believed to relieve N/V by direct local action on the GI tract wall, to decrease smooth muscle contraction and delay gastric emptying.^{26,27}

Alternatively, concentrated cola syrup, which also contains the sugars and phosphoric acid that are in PCS, has been used. Because commercially available carbonated cola beverages often have a 5:1 water-to-syrup ratio, substituting such drinks, even if allowed to go “flat,” is not recommended. In adults, PCS should be given at a dosage of 15–30 mL every 15 minutes until distress subsides. Taking more than 5 doses in 1 hour is not recommended. Children 2–12 years of age can take 5–10 mL every 15 minutes. Dosing fluids should not be diluted, and intake of other fluids should be avoided immediately before or after taking PCS.²⁶

Possible adverse effects with PCS are stomach pain and diarrhea. Each 5 mL of PCS contains 3.74 g of total sugar,²⁶ so caution is indicated with use of this solution in patients with diabetes. Similarly, patients with hereditary fructose intolerance should avoid using PCS.

Product Selection Guidelines

Specific factors to be considered in the choice of antiemetic products include pregnancy and lactation status; patient age, especially with the pediatric and geriatric populations; and presence of any therapeutic limitations, such as hepatic or renal impairment. These factors may particularly affect drug

selection and dosing. Furthermore, the product should be compatible with the patient's lifestyle, concurrent medication use, sensitivity to certain product ingredients such as dyes or fructose, and preference for frequency of dosing. Hence, product selection guidelines should be relevant for special populations and other considerations, such as the potential for drug interactions, and should include patient preferences such as whether the product is liquid or chewable or contains alcohol (Table 19–5).

Table 19–5 Selected Nonprescription Antiemetic Products and Common Drug Interactions			
Antiemetic	Drug/Drug Class	Potential Interaction	Management and Prevention Measures
Bismuth subsalicylate	Tetracyclines (tetracycline, doxycycline, minocycline, demeclocycline)	Decreased antibacterial effect caused by impaired absorption	Avoid concurrent administration; take doxycycline 2–3 hours before bismuth subsalicylate.
	Warfarin	Increased risk of bleeding (elevations of INR)	Avoid concurrent use; monitor INR closely near times of administration and discontinuation of bismuth subsalicylate.
	Live vaccines containing varicella or influenza	Increased risk of Reye syndrome	Avoid concurrent administration with live vaccines.
Antihistamines (cyclizine, doxylamine, dimenhydrinate, diphenhydramine, meclizine)	Anticholinergics (ipratropium, tiotropium)	May increase anticholinergic adverse effects	Monitor for signs of altered mental status, dry skin, dry mouth, constipation, mydriasis, and tachycardia.
	Opioid-related agents (fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone)	May increase sedative adverse effects	Monitor for signs of respiratory suppression, sedation, and hypotension. Consider lower doses of the concomitant agents.
	Bupropion	May lower seizure threshold	Use lowest therapeutic dose of bupropion and

Antiemetic	Drug/Drug Class	Potential Interaction	Management and Prevention Measures
			increase slowly.
	Donepezil	May lower seizure threshold	Use lowest therapeutic dose of donepezil and increase slowly.
Ginger	Warfarin	Increased risk of bleeding (elevation of INR), possibly seen at higher doses of ginger exceeding 4 g/day	Avoid use of ginger if possible.
Pyridoxine	Altretamine	Reduced anticancer effects of altretamine	Avoid concurrent use.

Key: INR = International normalized ratio.

Source: References 2, 22, 26, and 37.

Special Populations

Pregnant Women. Several nonpharmacologic recommendations can be made to help control NVP ([Table 19–6](#)). In patients with typically mild symptoms, nausea can be avoided by eating frequent small meals and avoiding spicy or fatty foods or sensory stimuli that may provoke symptoms. Consumption of bland carbohydrates, such as crackers, and high-protein snacks may be beneficial, especially in the morning. However, published evidence supporting dietary changes for prevention of N/V is very limited. In patients with a history of NVP, the American College of Obstetricians and Gynecologists (ACOG) recommends taking a multivitamin for at least 1 month before planned conception to decrease the severity of NVP.²⁰ This measure may not be useful in pregnant patients presenting with nausea, but it may be an option for future preconception counseling.

Table 19–6 Nonpharmacologic Measures to Prevent Nausea and Vomiting of Pregnancy

- Take a prenatal multivitamin for 1 month before planned conception.

- Before getting out of bed, eat several dry crackers and relax in bed for 10–15 minutes.
- Get out of bed very slowly and do not make any sudden movements.
- Before eating breakfast, nibble on dry toast or crackers.
- Make sure there is plenty of fresh air in the area where meals are prepared and eaten.
- Eat small meals every 1–2 hours to avoid a full stomach.
- Avoid areas of excessive heat or humidity.
- When nauseated, try small sips of carbonated beverages or fruit juices.
- Avoid greasy or fatty foods such as fried foods, gravy, mayonnaise, and salad dressing, as well as spicy or acidic foods (citrus fruits and beverages, tomatoes).
- Avoid sensory stimuli such as odors, noises, or flickering lights.
- Avoid iron-containing supplements.
- Eat dry, bland, and high-protein foods.

Source: References 17 and 28.

Evidence exists to support the use of nonprescription antiemetics, such as doxylamine and pyridoxine, for NVP.²⁸ ACOG recommends pyridoxine with or without doxylamine as first-line pharmacotherapy for NVP.²⁰ Additionally, the use of doxylamine and pyridoxine preemptively may reduce the recurrence of symptoms.²⁸ Pyridoxine also is excreted in breast milk. Extremely high doses of pyridoxine (600 mg/day) may inhibit prolactin secretion.²⁹ Other antihistamines, such as dimenhydrinate and diphenhydramine have been shown to be effective in controlling NVP, with no association with the development of birth defects.²⁰ (Please refer to the Preface for a detailed explanation of the pregnancy data.) Of note, ginger may be as effective as pyridoxine for treating NVP. Some evidence supports the safety of ginger for pregnant women, with no significant increase in risk for spontaneous abortion, congenital malformation, or low birth weight.^{30,31} (See [Chapter 51](#) for further discussion of this treatment.)

Geriatric Patients. Antihistamines should be used with caution in patients of advanced age because of the associated increased risk of adverse effects. The anticholinergic and sedative effects may not be tolerable in this patient population. The American Geriatrics Society considers these medications potentially inappropriate and strongly recommends avoiding use of antihistamines in persons of advanced age.³² In addition, a comprehensive medication review may be necessary for patients in this age group to identify

and resolve any potential drug-related problems, including drug interactions.

PCS may be used if the patient does not have uncontrolled blood glucose levels or hereditary fructose intolerance. Neither acupressure nor any acustimulation product, such as acupressure bands, should be used in patients with pacemakers. Other nonpharmacologic options such as avoidance of trigger foods and scents also could be considered.

Lactating Women. Antihistamines may adversely affect the mother's milk supply, so nursing mothers should not use these agents. For bismuth subsalicylate (BSS), it is estimated that less than 1% of maternal dose is absorbed by the infant. Alternatives to BSS are preferred for lactating women.³³ Little evidence is available to support the safety of the use of ginger by lactating women.³⁴

Pediatric Patients. In newborns and older infants, vomiting may lead rapidly to dehydration and acid–base disturbances. Vomiting is different from simple regurgitation, which is common in infants, in being more forceful and producing larger amounts of emesis. In newborns, vomiting may be caused by GI tract obstruction. In infants, vomiting may be a sign of gastroesophageal reflux disease (GERD).³⁵ N/V can occur in children for a variety of reasons, including GI obstruction, CNS abnormalities, and infection.³⁶

The Centers for Disease Control and Prevention (CDC) classifies dehydration in children as mild if less than 3% of body weight is lost, moderate if 3%–9% is lost, and severe if greater than 9% is lost.¹³ Moderate to severe cases of dehydration warrant a medical referral. Mild to moderate dehydration can be managed with oral rehydration therapy as described in this chapter and in [Chapter 16](#). Antihistamines may diminish mental alertness and occasionally produce paradoxical excitation in young children.²² BSS is not recommended in children or teenagers who have or are recovering from chickenpox or an influenza-like illness because of the risk of Reye syndrome.³⁷ (See [Chapter 5](#), subsection “Salicylates” for further information.)

Complementary Therapies

Some evidence supports the use of ginger, pyridoxine (vitamin B₆), and acupressure bands in the treatment of nausea.

Ginger

Ginger (*Zingiber officinale*) has been used for nausea related to pregnancy, motion sickness, and surgery.³⁸ A 2015 Cochrane review of this use of ginger found limited and inconsistent evidence for its efficacy, although several studies suggested that ginger may be superior to placebo in preventing NVP.³⁹ The review reported no difference in rates of spontaneous abortion, congenital abnormalities, or other fetal adverse outcomes, although the included studies may have had insufficient power.³⁹ Other data regarding the safety of the use of ginger in pregnancy are limited. Larger doses of ginger may lead to mild adverse GI effects, including heartburn, belching, and discomfort.³¹ Some evidence suggests that ginger may have anticoagulant and hypotensive effects.

Ginger can be given at 250 mg up to 2 g daily in 3–4 divided doses, although it appears that doses of approximately 1 g/day are more effective than placebo.³¹ Ginger may be as effective as pyridoxine for treating N/V. Compared with dimenhydrinate, ginger may cause fewer adverse effects.³⁰ (See [Chapter 51](#) for an in-depth discussion of use of ginger as a herbal product.)

Most ginger ale drinks are artificially flavored or contain amounts of ginger that are too insignificant to be therapeutic.

Pyridoxine (Vitamin B₆)

Pyridoxine is a water-soluble B vitamin that is important in various metabolic functions, including protein metabolism, hemoglobin synthesis, and neurotransmitter function.²⁹ The Dietary Reference Intake of pyridoxine for healthy adults is 1.3–2 mg/day. Pyridoxine may be useful in NVP. Typical dosing of pyridoxine for relief of nausea is 10–25 mg 3 times a day.

Pyridoxine generally is well tolerated. Large doses (>200 mg/day) of pyridoxine over longer periods of time (>2 months) may result in adverse effects such as peripheral neuropathy, weakness, lethargy, and nystagmus.

Pyridoxine has had mixed results for efficacy in treating N/V. Overall data suggest that pyridoxine is effective.²⁹ NVP is an off-label indication for pyridoxine. Pyridoxine is available as a combination product with doxylamine, available by prescription.⁴⁰

Acupressure

The use of acupressure involves direct pressure on the pericardium-6 (P6) point on either wrist. The P6 point is located approximately three fingerwidths from the middle crease of the wrist (see <https://exploreim.ucla.edu/self-care/acupressure-point-p6/>). Pressure can be applied between the two tendons using either the finger or a wristband. Acupressure at P6 may be more effective for prevention of postoperative N/V than for treating NVP.⁴¹ The “dosing” for acupressure can vary widely, ranging from as-needed, to 10 minutes 3 times a day, to continuous pressure. The different dosing regimens have shown mixed results for efficacy.⁴¹

Cannabinoids

Oral cannabinoids, available by prescription, may have similar efficacy against N/V to that of conventional prescription antiemetics.⁴² Users of cannabidiol (CBD) oil may perceive benefits for its use as an antiemetic.^{43,44} Caution is indicated in recommending CBD, however, because standardization of such products is lacking. In 2018, the Agriculture Improvement Act (Farm Bill) removed products that contained no more than 0.3% of low-tetrahydrocannabinol (THC), such as CBD, from the definition of marijuana, a schedule I drug.⁴⁵ Studies on the safety and quality of CBD are lacking, and FDA is working to answer questions about its safety and good manufacturing practices. Patients should be aware of the potential risks of liver injury, drug interactions, and male reproductive toxicity that are associated with use of CBD products.⁴⁶ FDA also is exploring lawful marketing of CBD products.⁴⁶

Algorithm: N/V in Adults

Figure 19–1 Self-care for N/V in adults. Key: AH = Antihistamine; B6 = pyridoxine; BG = blood glucose; BPH = benign prostatic hyperplasia; CNS = central nervous system; DKA = diabetic ketoacidosis; GERD = gastroesophageal reflux disease; GI = gastrointestinal; HHS = hyperosmolar hyperglycemic syndrome; H2RA = histamine type 2 receptor antagonist; NSAID = nonsteroidal anti-inflammatory drug; N/V = nausea and vomiting; ORS = oral rehydration solution; PCP = primary care provider.

Algorithm: N/V in Children

Figure 19–2 Self-care for N/V in children. Key: AH = Antihistamine; CNS = central nervous system; GI = gastrointestinal; N/V = nausea and vomiting; ORS = oral rehydration solution; PCP = primary care provider.

Assessment of Nausea and Vomiting: A Case-Based Approach

Vomiting is a symptom produced not only by benign processes but also by serious illnesses, and it may lead to various complications. Physical assessment of the patient may help to determine whether such complications, as listed in the section “Clinical Presentation of Nausea and Vomiting” have occurred. Important factors in this assessment are the patient’s general appearance, mental status, and volume status and the presence and severity of any abdominal pain. Evaluation of vital signs such as blood pressure, heart rate, temperature, and weight also is pertinent. Recognition of concurrent signs and symptoms is essential to identify the likely etiologic condition. With acute onset of vomiting, it is vital to determine whether a toxin could be the cause. In such cases, careful questioning of the patient or caregiver about possible ingestion or exposure, especially in preschoolers and adolescents, often will reveal the responsible toxin. Detailed information about the patient’s medical history related to the GI tract is especially helpful in determining potential causes.

A major concern with vomiting is the loss of fluids and the inability to eat or drink. This situation may result in dehydration and electrolyte disturbances. Self-care is inappropriate for patients with dehydration, severe anorexia, weight loss, or poor nutritional status. Medical evaluation for dehydration is indicated when severe vomiting or diarrhea persists for more than several hours in children or for 48 hours in adults.^{2,4,13}

The health care provider should be aware that some patients may use nonprescription antiemetics for self-treatment in the early stages of a serious illness. To avoid potential additive toxicity, it is essential to identify what

products the patient has already used for symptom relief. Many patients choose to self-medicate with various nonprescription products to avoid a medical office visit. Caution is warranted, however, in recommending self-medication for N/V symptoms, and a crucial component of assessment with N/V is determining whether medical referral is indicated.

Cases 19–1 and 19–2 provide examples of assessment of two different patients presenting with vomiting.

Case 19–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient has complained of being nauseous for the past week, especially during late morning, but it persists through most of the day. She has vomited twice during that time. She has maintained her appetite.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Symptoms are worse in the morning or when she smells food cooking. She also is symptomatic at work.
c. Description of the patient's efforts to relieve the symptoms	The patient eats a few crackers with a few sips of ginger ale at home. At work she goes to the restroom and closes her eyes for a few minutes.
d. Patient's identity	Alicia Franklin
e. Patient's age, gender, height, and weight	27 years, female, 5 ft 7 in., 150 lb

Relevant Evaluation Criteria	Scenario/Model Outcome
f. Patient's occupation	Graphic designer
g. Patient's dietary habits	Balanced diet with plenty of fruits and vegetables. Patient is able to eat well between nausea episodes.
h. Patient's sleep habits	Averages 7-8 hours per night.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Patient has no chronic conditions. She just found out she is 9 weeks pregnant and began a prenatal vitamin. She denies use of dietary supplements.
j. Allergies	None
k. History of other adverse reactions to medications	None
l. Other (describe) -----	n/a
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Nausea persisting throughout the day; occasional vomiting. She does not like the smell of certain foods; NVP is likely.
3. Identify exclusions for self-treatment (Figure 19-1).	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this	Options include (1) Recommend self-care with- Nondrug strategies (dietary and environmental changes [Table 19-6])- Acupressure or acustimulation bands- OTC pyridoxine- OTC doxylamine- OTC phosphorated carbohydrate solution- Ginger

Relevant Evaluation Criteria	Scenario/Model Outcome
information with the patient or caregiver.	(2) Recommend lifestyle modifications until a health care provider can be consulted. (3) Make a medical referral. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Because the patient does not appear dehydrated and can drink small amounts of ginger ale and can tolerate crackers, encourage her to continue to take sips of liquids and eat small meals. She does not have signs/symptoms of dehydration, such as tachycardia, decreased skin turgor, noticeable weight loss, or clothes that fit loosely. She can try doxylamine 12.5 mg 3 times a day and vitamin B ₆ 10 mg 3 times a day. Other nonpharmacologic suggestions in Table 19–6 should be followed. If symptoms persist, she should consult her provider.
6. Describe the recommended therapeutic approach to the patient or caregiver.	“You probably have nausea and vomiting of pregnancy, or NVP. You can take vitamin B ₆ orally every 8 hours. In addition, you may add doxylamine 12.5 mg orally every 8 hours. You also may benefit from other nonpharmacologic techniques (Table 19–6), such as continuing to eat crackers or eating bland foods in the morning before arising, sleeping in a well-ventilated room, and avoiding strong odors. If you do not feel better, you may want to contact your regular health care provider.”
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	“The American College of Obstetricians and Gynecologists states that doxylamine plus vitamin B ₆ , up to 3 tablets daily, may help your symptoms. Because you are able to drink fluids and are not dehydrated, seeking medical care may not be necessary at this time. However, if nausea or vomiting worsens, medical attention for further evaluation is necessary.”
Implement	
8. When recommending self-	

Relevant Evaluation Criteria	Scenario/Model Outcome
care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
a. Appropriate dose and frequency of administration	"Add vitamin B ₆ 10 mg combined with 12.5 mg of doxylamine (½ of a 25 mg tablet). Doxylamine is available in the United States as a nonprescription sleep aid (doxylamine succinate [Unisom SleepTabs] 25 mg)."
b. Maximum number of days the therapy should be employed	"There are no limits to the number of days that vitamin B ₆ and doxylamine can be taken. Nausea associated with pregnancy typically resolves after week 16."
c. Product administration procedures	"Take vitamin B ₆ and doxylamine with a small glass of water 3–4 times a day."
d. Expected time to onset of relief/degree of relief that can be reasonably expected	"Expected time to onset of relief and degree of relief are variable for all products and measures."
e. Most common adverse effects	"Vitamin B ₆ is not likely to cause any adverse effects. Drowsiness is the most common side effect of doxylamine; therefore, it is important not to drive or operate machinery while taking doxylamine. Other possible adverse effects include dry mouth, dry eyes, nasal congestion, urinary retention, and constipation."
f. Patient options in the event that condition worsens or persists	"Medical attention is necessary if the NVP does not subside or if adverse effects from the nonprescription product occur."
g. Product storage requirements	"Store this product at 59°–86°F."
h. Specific nondrug measures	See Table 19–6 for dietary and other measures.
Solicit follow-up	(1) "Will any of these products hurt my baby?"

Relevant Evaluation Criteria	Scenario/Model Outcome
questions from the patient or caregiver.	
	(2) "What other products could I use instead?"
Answer the patient's or caregiver's questions.	(1) "These products have been used by many other pregnant women and have not caused harm to the mother or baby. Pregnant women have been exposed to these products hundreds of thousands of times without evidence of harm to the baby."
	(2) "Another product used for nausea during pregnancy is an acupressure band that is worn on the wrist for a short period of time, such as 5 minutes, or throughout the day. Ginger also can be considered. Phosphorated carbohydrate solution also may be tried. If these products do not work, then you will need medical attention to obtain a prescription product for your nausea."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Monitor for episodes of nausea and vomiting.

Key: n/a = Not applicable; NVP = nausea and vomiting of pregnancy; OTC = over-the-counter.

Case 19–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the	

Relevant Evaluation Criteria	Scenario/Model Outcome
patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient is a child who has vomited 6 times in the past 12 hours. The child has been crying and is inconsolable for about 20 minutes around each vomiting episode. Tears are not present with crying.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Symptoms worsen when the patient's mother attempts to provide grape juice.
c. Description of the patient's efforts to relieve the symptoms	Patient's mother tried to get him to eat a few bites of cereal and drink juice.
d. Patient's identity	Hunter Neilson
e. Patient's age, gender, height, and weight	16 months, male, 23 in., 20 lb (23 lb on previous day)
f. Patient's occupation	n/a
g. Patient's dietary habits	Normal healthy diet; consists of cereals, mashed vegetables, pasta, rice, chicken, yogurt, milk, and juice.
h. Patient's sleep habits	Up at 7:00 AM; in bed at 7:30 PM; naps for 2 hours, 1-3 PM.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Children's multivitamin with fluoride; patient is current with all recommended childhood vaccines, including rotavirus.
j. Allergies	Eggs: stomach upset
k. History of other adverse reactions to medications	None

Relevant Evaluation Criteria	Scenario/Model Outcome
I. Other (describe) -----	n/a
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Patient has had several episodes of vomiting. He is drowsy and unusually lethargic, and his body is floppy when he is held. The child appears to be dizzy when he stands up, and his abdomen seems somewhat flat. His mother reports he has had a dry diaper for most of the day. When the child cries, few tears are noted. He appears dehydrated and may have viral gastroenteritis.
3. Identify exclusions for self-treatment (Figure 19-2).	The patient is severely dehydrated (Table 19-2), as evidenced by signs and symptoms including weight loss of >9%.
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Recommend that the patient's mother administer- an OTC ORS- an OTC phosphorated carbohydrate solution- an acupressure band (2) Recommend that the patient's mother administer self-care modalities until an appropriate health care provider can be consulted. (3) Refer the patient for further medical evaluation. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient or caregiver preferences.	Hunter is unable to drink small amounts of fluid or eat small amounts of food (cereal). He also has signs/symptoms of dehydration (appears drowsy and lethargic; has a floppy body, dizziness, flat abdomen; has lost 3 lb, approximately 13% of his body weight since the previous day; has a dry diaper and sheds few tears). On the basis of these signs/symptoms, Mrs. Neilson should immediately take the child for medical evaluation and attempt to administer small sips of ORS fluid on the way to urgent or emergency care.

Relevant Evaluation Criteria	Scenario/Model Outcome
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Your child needs to be seen by an appropriate health care provider because he appears dehydrated. Please have someone drive you and Hunter to the urgent care facility. On the way, administer 1 teaspoonful of ORS fluid, not grape juice, every 1-2 minutes."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Hunter's signs and symptoms (floppy body, flat abdomen, weight loss, dry diaper, few tears) indicate that he is dehydrated. Because he has been unable to drink sufficient fluids or eat anything to counter the dehydration, he needs medical attention."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	"Oral rehydration solutions such as Pedialyte are not the same as sports drinks such as Gatorade or Powerade. If all that is available is a sports drink, mix with water to one-half strength and offer 1 teaspoonful every 5 minutes."
Solicit follow-up questions from the patient or caregiver.	"Is there a nonprescription medication that might work so that I don't have to take Hunter to the urgent care?"
Answer the patient's or caregiver's questions.	"No. Hunter is dehydrated; he needs urgent medical care so that he can feel better and get well, without serious complications."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Provider should contact Mrs. Neilson to monitor for signs of dehydration, including weight loss, and for resumption of normal behaviors and activities.

Key: n/a = Not applicable; ORS = oral rehydration solution; OTC = over-the-counter.

Patient Counseling for Nausea and Vomiting

The health care provider should stress that treatment for N/V must focus on identifying and, if possible, correcting the underlying cause. Patients prone to overeating, eating disorders, or motion sickness should be advised to avoid behaviors or situations that lead to N/V. An important point to emphasize in patient counseling is that acute vomiting typically requires only symptomatic treatment, because the problem usually is self-limiting and will resolve spontaneously. If the cause of the N/V symptoms is known and self-treatment with nonprescription medication is appropriate, proper use of the recommended product should be explained. Patient education also should include information about possible adverse effects of recommended products, as well as signs and symptoms indicating that further medical attention is warranted. The box “Patient Education for Nausea and Vomiting” lists specific information to provide in patient counseling.

Evaluation of Patient Outcomes for Nausea and Vomiting

After the provider has provided information on or suggestions for self-management and treatment for N/V, follow-up assessment of the patient should occur within 24 hours of the initial encounter. A validated assessment tool, established by Rhodes and McDaniel, can be used to monitor clinical status; this tool is available at <https://helper.org/downloads/rhodes-index.pdf>.⁴⁷ The follow-up evaluation should ascertain whether the N/V has diminished or abated; whether the patient has any residual signs or symptoms, especially those related to dehydration; whether abnormalities in vital signs, such as tachycardia, have returned to normal; and whether the patient is afebrile. If the patient had prolonged N/V (>24–48 hours) or experienced a change in or worsening of symptoms that required immediate referral for medical evaluation, follow-up contact is indicated to determine whether the patient sought medical help and what type of treatment was administered. It also is important for the provider to assess whether any further counseling is needed or if the patient has additional questions. The provider also can use this opportunity to provide reassurance and support.

Patient Education for Nausea and Vomiting

The objectives of self-treatment are (1) to improve the symptoms of occasional, self-limited nausea and vomiting (N/V), (2) to identify and correct the underlying cause, (3) to prevent and correct complications of vomiting, and (4) to prevent future occurrences. For most patients, carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

Nondrug Measures

- To prevent N/V in pregnancy, eat small, frequent meals that are low in fat content. Sleep in a room with fresh air. Also, try eating crackers or a high-protein snack before getting up in the morning. Try lying down to relieve the symptoms once they occur ([Table 19–6](#)).
- To prevent motion sickness in young children, place them in a car seat that allows them to look out the windows ([Table 19–3](#)). Try acupressure wristbands to prevent motion sickness in adults or older children.
- To prevent nausea associated with overeating, consume foods and beverages in moderation, and avoid foods or beverages known to cause nausea.

Nonprescription Medications

Antacids, Histamine Type 2 Receptor Antagonists (H2RAs), and Bismuth Subsalicylate

- Take antacids, H2RAs (e.g., ranitidine or famotidine), or bismuth subsalicylate for nausea caused by overeating. Follow product instructions for dosages. (See [Chapters 13](#) and [16](#) for additional information on these medications.)

Phosphorated Carbohydrate Solution

- Take phosphorated carbohydrate solution for nausea and vomiting

associated with upset stomach caused by viral gastroenteritis, food indiscretions, and pregnancy.

- Give 1–2 tablespoonsful (15–30 mL) of the solution to adults at 15-minute intervals until vomiting stops. For children ages 2–12 years of age, give 1–2 teaspoonful (5–10 mL). Do not give more than 5 doses in 1 hour.
- Do not dilute the solution, and do not allow the patient to consume other liquids for 15 minutes after taking a dose.
- Patients with hereditary fructose intolerance should not take this product.
- Patients with diabetes should consult their medical provider before taking this product.

Antihistamines

- Take antihistamines for self-treatment of N/V caused by motion sickness.
- To prevent motion sickness, take antihistamines at least 30–60 minutes before departure. Continue taking the medication during travel. Follow the dosage guidelines in [Table 19–5](#).
- While using antihistamines, avoid driving or operating hazardous machinery or engaging in tasks that require a high degree of mental alertness. Drowsiness is the most common adverse effect of these medications.
- Patients with asthma, narrow-angle glaucoma, obstructive disease of the gastrointestinal or genitourinary tract, or benign prostatic hypertrophy should consult an appropriate health care provider before using antihistamines.
- Caution patients that antihistamines may increase the sedative effects of alcohol, tranquilizers, hypnotics, and sedatives. Antihistamines may produce excitability in children or mental confusion in persons of advanced age.
- Do not take oral diphenhydramine products if topical (external) diphenhydramine preparations are being used.

Oral Rehydration Solution (ORS)

- If needed, take an ORS to prevent dehydration secondary to vomiting and diarrhea.
- Consider placing the ORS in the refrigerator to improve taste. Alternatively, the patient can use ORS freezer pops or another dosage form to improve palatability.

When to Seek Medical Attention

- Seek medical attention if you notice signs and symptoms of serious dehydration associated with N/V.
- Seek medical attention if vomiting does not stop after 5 doses of phosphorated carbohydrate solution.

Key Points for Nausea and Vomiting

- N/V are manifestations of an underlying disorder or disturbance; therefore, treatment should focus on identifying and correcting the underlying cause.
- Nonprescription antiemetic medications are suitable for preventing and controlling the symptoms of occasional self-limiting N/V.
- Overeating, food poisoning, viral gastroenteritis, and motion sickness may cause self-limiting N/V.
- Antacids, nonprescription H₂RAs, or PCS may help to relieve symptoms associated with indigestion from overeating.
- Antihistamines are the agents of choice to treat N/V secondary to motion sickness. Second-generation antihistamines, however, are ineffective in treating N/V.
- Methods and agents that are safe for treating NVP and N/V in most patients 2 years of age and older include use of acupressure/acustimulation devices and PCS.

- Uncomplicated NVP may be treated with pyridoxine, doxylamine, PCS, ginger, or acupressure/acustimulation devices.
- Loss of fluids and the inability to eat or drink due to N/V may result in dehydration associated with electrolyte disturbances. This primary complication of N/V should be treated with ORS therapy.
- A patient who presents with complications related to N/V may not be a candidate for self-treatment but instead should be referred for medical evaluation.

Chapter 20: Prebiotics and Probiotics

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In today's climate of self-management for optimal health and wellness, use of prebiotics and probiotics has become increasingly popular. Multiple studies have confirmed their beneficial effects on various aspects of gastrointestinal (GI) tract function, as well as in treatment and prevention of certain disorders, although much remains to be elucidated. In brief, *prebiotics* are substrates selectively utilized by host microorganisms—the enteric microflora—to support gut health, and *probiotics* are nonharmful living microorganisms also recognized to have beneficial health effects when ingested in sufficient amounts. A basic understanding of GI microflora characteristics, summarized next, is recommended for health care providers to assist patients in the selection or use of appropriate prebiotic and probiotic products.

The Gut Microbiota

The microflora of the GI tract is known as the enteric *microbiota*. The GI tract hosts approximately 300–500 species of commensal bacteria, with concentrations of up to 10^9 colony-forming units (CFU)/mL in the terminal ileum and 10^{12} CFU/mL in the colon.¹ In composition, however, the enteric microbiota may be far more diverse than has been recognized to date. Only within the past 20 years or so have the GI microbiota and its role in human health and disease been explored in earnest. The extent of microbiota influence on health maintenance and disease development appears to be significant. Although understanding of the complex interactions between the GI tract and enteric microbiota remains incomplete, the paradigm of human biology is shifting to embrace the ecology of the individual, including processes of transgenomic and epigenomic co-metabolism with that person's unique GI microbiome.^{2,3} More recently, a view of the microbiome as a “superorganism” in a symbiotic relationship with the gut mucosa has been advanced.⁴

Prebiotics

Prebiotics support the enteric microbiota and typically are substances fermented in the colon. As noted, they are substrates that are selectively utilized by host microorganisms, conferring a health benefit. Some types of fiber act as prebiotics. The undigested fiber enters the colon and is fermented by bacteria, primarily bifidobacteria and lactobacilli. Fermentation products, including short-chain fatty acids (acetate, butyrate, and propionate) and lactate, produce an environment favorable to growth of these beneficial bacteria. To be considered a prebiotic, fiber must selectively stimulate the growth and/or activity of one or a limited number of health-promoting bacterial species residing in the colon and benefit the host.^{1,4-6}

Sources and Intake

Inulin-type fructans, including their partial hydrolysis product fructooligosaccharides (FOS), are the most common prebiotics.⁷ These substances are found in small amounts in asparagus, bananas, chicory, Jerusalem artichoke, leek, onion, soy, and wheat.⁶ Inulin-type fructans are isolated from such sources and added to foods to attain concentrations contributing to prebiotic effects. Other sources of prebiotics are conjugated linoleic acid, polyunsaturated fatty acid, and human milk oligosaccharides.^{7,8}

Health Effects

Both inulin-type fructans and FOS significantly increase bifidobacteria in the human gut.^{7,8} Doses vary greatly in studies. The use of prebiotics generally should not result in adverse effects such as abdominal distention and discomfort.

Beneficial effects of prebiotics supported by some human data include stool bulking and decreased constipation, better absorption of calcium and magnesium, reduced triglycerides in mildly hypercholesterolemic persons, and stimulation of bifidobacteria growth.^{4,8,9} Studies using prebiotics for treatment or prevention of diarrhea have yielded conflicting results, which may depend on the underlying disorder.⁹ Improved vaccine response, decreased GI infections, stimulation of intestinal hormonal peptides, clinical improvement in inflammatory bowel disease (IBD), and reduced tumor growth are other possible benefits of prebiotics. Some beneficial effects may be enhanced with synbiotics, a mixture of both prebiotics and probiotics that together appear to improve health and well-being.⁶

Probiotics

As noted earlier, probiotics are nonpathogenic, living microorganisms that have a beneficial effect on the host when consumed in adequate amounts.^{1,6,10} These products must withstand the stresses inherent in processing, storage, and delivery without degradation, and the probiotic microorganisms must survive gastric acidity, bile acid lysis, and pancreatic enzyme digestion.^{4,5} Lactic acid-producing bacteria, especially those of the genera *Lactobacillus*, *Bifidobacterium*, and *Streptococcus*, are most often used in commercially available foods and for studies. Beyond early infancy, these microorganisms do not permanently colonize the GI tract and must be ingested regularly in sufficient quantity to maintain their presence. When such bacteria are present in adequate or optimal numbers, colonization by pathogenic organisms is reduced and mucosal defenses in the GI tract are enhanced. **Table 20–1** lists possible protective effects of probiotics and postulated mechanisms of action.^{4,9,11} For health care providers attempting to interpret data in the clinical setting, caution is warranted: Multiple species and strains of common probiotic bacteria exist, and effects cannot be extrapolated across species or even across different strains.⁶ Dosing may explain variance in treatment response in published studies. The optimal dose for a given probiotic is not known; however, studies showing efficacy typically use a minimum of 10⁷–10¹⁰ CFU per dose or 10⁸–10¹⁰ CFU daily.^{6,12} In a dose-ranging study, the probiotic capsule dosage form used exhibited poor dissolution characteristics, leading to reduced probiotic efficacy at higher doses relative to that at lower doses.¹³ This finding demonstrates the need to be vigilant in choosing an appropriate probiotic formulation that has been studied in patients.

Table 20–1 Possible Protective Effects of Probiotics	
Effect of Probiotic	Possible Mechanism(s)
GI Barrier Function	
Induce production of protective cytokines mediating EC regeneration and inhibiting apoptosis	Action through TLRs; intestinal homeostasis and EC protection requires recognition of commensal bacteria by TLRs
	Induction of IL-6

Effect of Probiotic	Possible Mechanism(s)
Redistribute and increase expression of factors involved in maintaining EC tight junctions	Altered protein kinase C signaling
Counteract effects or inhibit production of inflammatory cytokines associated with increased EC permeability	IL-10 upregulation (regulatory cytokine)
	Reduced effect of TNF-alpha and INF-gamma
	Reduce TNF-alpha production
	Stimulation of IgA secretion
Antimicrobial Activity	
Inhibit growth of potential pathogens	Decreased luminal pH
	Production of bactericidal proteins (bacteriocins)
Inhibit adhesion of pathogenic bacteria to EC	Increased mucin production
	Reduced transepithelial resistance associated with binding of some pathogens
	Competitive exclusion of pathogens from EC surface binding sites due to nonspecific binding associated with the hydrophobic cell surface properties; mucus-binding pili enhance binding to mucosal surface
	Binding to pathogenic microorganisms, thereby preventing interaction between the microorganism and EC surface
Influence production of cryptdins by Paneth cells	Antibacterial action of cryptdins
Alter virulence	Altered secretion of molecules influencing expression of genes controlling virulence
EC Inflammatory Responses	
Alter EC cytokine production	Downregulation of bacteria-induced protein kinase C and IL-6

Effect of Probiotic	Possible Mechanism(s)
	Inhibition of TNF-alpha-induced IL-8 production
	Downmodulation of genes associated with proinflammatory signal induction
	Attenuation of nuclear factor-kappa B activation
Lymphoid Cell	
Enhance antiviral activity	Inhibition of T-cell proliferation
	Induction of macrophages to express increased amounts of inflammatory cytokines and nitric oxide
	Stimulation of granulocyte colony-stimulating factor release by macrophages
	Increased natural killer T-cell activity
Activate macrophages	Increased antigen presentation to B lymphocytes
Regulatory T-Cell Induction	
Increase CD4+ (regulatory) T cells with cell-surface TGF-beta (regulatory cytokine)	Monocyte-derived dendritic cells inducing IL-10 production by T cells

Key: EC = Epithelial cell; GI = gastrointestinal; IgA = immunoglobulin A; IL = interleukin; INF = interferon; TGF = transforming growth factor; TLR = Toll-like receptor; TNF = tumor necrosis factor.

Source: References 1, 4–7, and 9.

Sources

Many traditional foods are fermented by bacteria and contain high concentrations of lactobacilli. Corn, cassava, millet, leafy vegetables (cabbage), and beans commonly serve as basic foodstuffs for fermentation. A few fermented foods are occasionally eaten in the United States, such as brined olives, kimchi (Korean fermented cabbage), miso, sauerkraut, and tempeh;

however, the major food source of probiotic bacteria is “cultured” dairy foods. Many major brands of yogurt contain probiotic bacteria, although viable cultures are not required for yogurt in the United States, and labels do not list the number of viable probiotic organisms. Liquid yogurt drinks (kefir) and cultured fluid milk, such as sweet acidophilus milk and buttermilk, can contain variable amounts of viable organisms; however, most provide adequate amounts (10^8 viable organisms per g of product). With the expanding interest in probiotics, new products with added probiotic organisms are appearing regularly, sometimes with limited or no data on the organisms contained or on the efficacy of the combinations used.

Health Effects

Interest in probiotics has increased dramatically in the past decade. Research covers a wide range of disease states and subjects of all ages (premature neonates to the older adult). Clinical data, for the most part, are preliminary; however, moderate-quality evidence supports the use of probiotics to prevent or treat certain gastrointestinal disease states, as well as metabolic and respiratory syndromes, and to modify cardiovascular risk factors. In addition to the indications for probiotics with robust evidence, as discussed thus far, [Table 20–2](#) also includes additional indications for probiotics and associated organisms. Results may be influenced by the dose, frequency of dosing, and/or organisms in any specific probiotic product. Most studies have been small and have used isolated bacteria (classified as nutritional supplements) or foods with added probiotics, rather than foods that naturally contain the beneficial bacteria.

Table 20–2 Uses of Probiotics

Condition/ Disease	Probiotics and Dosages	Comments
Allergy		
Atopic dermatitis in infants, prevention and treatment	<i>L. rhamnosus</i> GG 10^{10} CFU daily for 2–4 weeks before delivery, then infant administration	Conflicting results; several studies show decreased severity; most studies were small limited studies with good design and adequate power to support effectiveness for atopic eczema associated with cow milk allergy. Meta-analysis indicated reduced frequency of eczema with selected probiotics supplied to mothers in the third trimester or during breastfeeding, or to their infants. With recognized high risk for

Condition/ Disease	Probiotics and Dosages	Comments
	for 6 months	atopic dermatitis, probiotic administration to the mother during pregnancy and to the infant for several months after birth, under the supervision of a health care provider, may be of benefit.
Diarrhea		
Acute, non-antibiotic- associated treatment in pediatrics and infants	<i>L. rhamnosus</i> GG at least 10 ¹⁰ CFU in 250 mL of oral rehydration solution; 10 ¹⁰ -10 ¹¹ CFU twice daily for 2-5 days	Multiple studies and meta-analyses; duration of diarrhea was reduced by about 1 day. Evidence of benefit is stronger for viral gastroenteritis than for bacterial infection. Timing of administration may affect efficacy. Evidence is stronger for treatment than for prevention.
	<i>L. reuteri</i> 10 ¹⁰ -10 ¹¹ CFU daily for up to 5 days	
Antibiotic- associated, prevention (not <i>Clostridioides</i> <i>difficile</i>)	<i>S. boulardii</i> 4 × 10 ⁹ -2 × 10 ¹⁰ CFU daily for 1-4 weeks	Multiple studies in both adults and pediatric patients have yielded some conflicting results; however, literature supports benefit overall.
	<i>L. rhamnosus</i> GG 6 × 10 ⁹ -4 × 10 ¹⁰ CFU daily for 1-2 weeks	
	<i>L. acidophilus</i> + <i>L. bulgaricus</i> 2 × 10 ⁹ CFU daily for 5-10 days	
	<i>L. acidophilus</i> + <i>B. longum</i> 5 × 10 ⁹ CFU daily for 7 days	

Condition/ Disease	Probiotics and Dosages	Comments
	<i>L. acidophilus</i> + <i>B. lactis</i> 1×10^{11} CFU daily for 21 days	
<i>Clostridioides difficile</i> infection	<i>S. boulardii</i> 2×10^{10} CFU daily $\times 4$ weeks with antibiotic therapy	Meta-analysis shows benefit. Promising role as adjuvant in treatment of recurrent <i>C. difficile</i> diarrhea.
Traveler's diarrhea	<i>L. rhamnosus</i> GG 2×10^9 CFU daily starting 2 days before and continued during travel	Results in randomized controlled studies are conflicting; modest positive results with some strains.
	<i>S. boulardii</i> 5×10^9 – 2×10^{10} CFU daily starting 5 days before and continued during travel	
Lactose intolerance	Yogurt with live cultures of <i>L. delbrueckii</i> + <i>Strep. thermophilus</i> $\geq 10^8$ CFU/g of yogurt	Reduced symptoms of lactose intolerance. Microbial beta- galactosidase improves lactose hydrolysis.
Radiation enteritis	<i>L. acidophilus</i> NDC01748 1.5×10^9 3 times daily for 7 days	A limited number of studies provide promising results; probiotic may reduce severity of diarrhea or improve stool consistency without decreasing the incidence of diarrhea. Overall, data are inadequate to establish effectiveness at this time.
	VSL#3 4.5×10^{11} CFU 3 times daily	

Condition/ Disease	Probiotics and Dosages	Comments
IBD		
Crohn's disease, induce and maintain remission	<i>S. boulardii</i> 1 g daily for 6 months with concurrent mesalamine	Small clinical studies, some with up to 1 year of follow-up; several randomized controlled trials, with equivocal results. Data are inadequate to establish effectiveness.
Pouchitis, preventing and maintaining remission	VSL#3 1.8×10^{12} CFU daily for 9–12 months	Meta-analysis data support probiotics for maintaining remission of chronic pouchitis. Inadequate studies to establish effectiveness for inducing remission or preventing pouchitis.
Ulcerative colitis	<i>E. coli</i> Nissle Active UC: 5×10^{10} CFU twice daily for up to 12 weeks, then 5×10^{10} CFU daily up to 12 months; Inactive UC: 5×10^{10} CFU daily for 12 weeks	Clinical evidence has not demonstrated benefit for inducing or maintaining remission. Some positive studies with similar efficacy to anti-inflammatory medications; however, data are inadequate to establish effectiveness.
	<i>S. boulardii</i> Active UC: 250 mg 3 times daily for 4 weeks with concurrent mesalamine	
	VSL#3 Active UC: 1.8×10^{12} CFU twice daily for 6 weeks with conventional therapy	
IBS		
Motility	VSL#3 9×10^{11}	May normalize muscle hypercontractility. Decreased bloating

Condition/ Disease	Probiotics and Dosages	Comments
disorders	CFU daily for 8 weeks	and flatulence in multiple studies; reduced abdominal pain or relief of constipation or diarrhea in some studies; however, other studies have yielded conflicting results. Most studies are small with an open label design. Meta-analyses demonstrate benefit in diarrhea, constipation, or IBS with mixed symptoms.
	<i>B. infantis</i> 10 ⁶ -10 ¹⁰ CFU daily for 4 weeks	
	<i>L. rhamnosus</i> GG + <i>L.</i> <i>rhamnosus</i> LC705 + <i>B.</i> <i>breve</i> + <i>P.</i> <i>freudenreichii</i> 8-9 × 10 ⁹ CFU daily for 6 months	
Infection		
<i>Helicobacter pylori</i>	<i>L. rhamnosus</i> GG 6 × 10 ⁹ CFU twice daily	Probiotic appears to reduce treatment-related side effects and to improve compliance. Meta-analyses indicate that probiotics may increase eradication when used with antibiotic therapy, especially in cases involving previous treatment failure.
	<i>B. clausii</i> 2 × 10 ⁹ spores 3 times daily	
	<i>S. boulardii</i> 2-4 × 10 ⁹ CFU/ day	
	<i>L. reuterii</i> 10 ⁸ CFU/day	
	Kefir 250 mL twice daily	
Vaginosis and vaginitis	<i>L. acidophilus</i> 8 oz yogurt containing	Decreased recurrence of vaginosis was shown in women with recurrent disease in one study; however, other studies have yielded conflicting results; evidence is inadequate to support

Condition/ Disease	Probiotics and Dosages	Comments
	≥10 ⁸ CFU/mL daily for 6 months	effectiveness.
	<i>L. rhamnosus</i> GR-1 + <i>L.</i> <i>fermentum</i> RC-14 10 ⁹ CFU in skim milk twice daily for 14 days	
	<i>L. rhamnosus</i> GG 10 ⁹ CFU per vaginal suppository twice daily for 7 days	
Intestinal Permeability		
NEC prevention	<i>B. bifidum</i> NCDO 1453, <i>L.</i> <i>acidophilus</i> NCDO 1748 10 ⁹ CFU twice daily	Strong support for effectiveness in preterm infants; meta-analysis supports supplementation of probiotics for reducing risk of severe NEC and death in premature infants.
	<i>L. acidophilus</i> + <i>B. infantis</i> 10 ⁸ CFU twice daily	
	<i>B. infantis</i> + <i>B.</i> <i>bifidum</i> + Strep. <i>thermophilus</i> 10 ⁹ CFU once daily	
Neurology		
Depression	<i>L. acidophilus</i> (2 × 10 ⁹), <i>L.</i> <i>casei</i> (2 × 10 ⁹),	Based on limited data, probiotics may be beneficial for reducing depression scores when given for add-on therapy with antidepressants for up to 8 weeks.

Condition/ Disease	Probiotics and Dosages	Comments
	<i>B. bifidum</i> , (2 × 10 ⁹)/g daily	
	<i>L. helveticus</i> + <i>B. longum</i> (≥2 × 10 ⁹)/g, 1.5 g sachet daily	
	<i>L. helveticus</i> + <i>B. longum</i> (≥2 × 10 ⁹)/g, 5 g sachet daily	
Multiple sclerosis	<i>L. acidophilus</i> , <i>L. casei</i> , <i>B. bifidum</i> , and <i>L. fermentum</i> (each 2 × 10 ⁹ CFU/g)	As suggested by limited data, probiotics may improve clinical and metabolic outcomes in multiple sclerosis.

^a VSL#3 contains four lactobacilli strains, three bifidobacteria strains, and *Streptococcus thermophilus*. VSL#3 is marketed as a probiotic medical food.

Key: *B.* = *Bifidobacterium*; CFU = colony forming units; *E.* = *Escherichia*; IBD = inflammatory bowel disease; IBS = irritable bowel syndrome; *L.* = *Lactobacillus*; NEC = necrotizing enterocolitis; *P.* = *Propionibacterium*; *S.* = *Saccharomyces*; *Strep.* = *Streptococcus*.

Source: References 1, 4, 6, 10, 18, 24, 25, 33, 40–42, 54, and 72–80.

Indications (With Available Data for Prebiotics)

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) comprises two disorders, ulcerative colitis (UC) and Crohn's disease (CD), both of which are relapsing and remitting inflammatory diseases. Both disorders may require costly therapies that are associated with potentially severe adverse effects. It is hypothesized that changes in the gut microbiota contribute to the inflammation within the GI

tract.¹⁴ Probiotics may restore the balance in microbiota and reduce the inflammatory response. Several strains of probiotics have been evaluated for the treatment of IBD, including *Lactobacillus* spp., *Bifidobacterium* spp., and multispecies products such as VSL#3, which contains four strains of *Lactobacillus* (*L. casei*, *L. plantarum*, *L. acidophilus*, and *L. delbrueckii* subsp. *bulgaricus*), three strains of *Bifidobacterium* (*B. longum*, *B. breve*, and *B. infantis*), and one strain of *Streptococcus* (*S. thermophilus*).^{14–17}

According to a meta-analysis of IBD data, probiotic therapy was better than placebo for reducing symptoms of UC but not for the induction of UC remission (relative risk [RR] 1.72, 95% CI 1.35–2.20; and RR 1.56, 95% CI 0.95–2.59, respectively).¹⁶ Continued treatment with probiotics in patients who achieved remission did not prevent relapses of UC (RR 0.97, 95% CI 0.78–1.20). This analysis included studies that used a variety of the probiotics previously mentioned. In a more recent meta-analysis, probiotics were not more beneficial than placebo in achieving remission of UC (RR for failure to achieve remission 0.86, 95% CI 0.68–1.08), with the exception of VSL#3, which outperformed placebo in 319 patients across three trials (RR 0.74, 95% CI 0.63–0.87).¹⁸ By contrast, probiotics were found to perform similarly to 5-aminosalicylate for the prevention of relapse of UC (RR 1.02, 95% CI 0.85–1.23). In this analysis, probiotics were not effective in inducing or maintaining remission of CD.

Patients with severe UC who require surgical colectomy may need an ileoanal anastomosis. After this procedure, symptoms of pouchitis, or inflammation of the surgically created pouch or artificial rectum, may develop in some patients. *Lactobacillus* GG did not alleviate acute pouchitis symptoms compared with placebo.¹⁷ VSL#3 performed better than placebo for the maintenance of remission of chronic pouchitis in an analysis of data for 76 subjects (RR 20.24, 95% CI 4.28–95.81). Findings regarding the prevention of pouchitis with VSL#3 appear to be equivocal. In contrast with UC, CD does not appear to be responsive to probiotics (RR 1.03, 95% CI 0.71–1.48).¹⁶ Additionally, prebiotics, such as FOS, inulin, and lactulose, have been evaluated for the treatment of UC and CD; however, on the basis of the limited data currently available, they do not seem to provide significant symptom reduction.¹⁹ Current UC treatment guidelines suggest the need for further study before the use of probiotics can be widely recommended.²⁰

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a functional GI disorder that manifests as a diarrhea- or constipation-predominant syndrome or as a mixed-symptom picture. IBS symptoms may be secondary to an imbalance in the composition of the GI microbiota, manifested as an increase in potentially harmful organisms (*Clostridium*, *Escherichia coli*, *Salmonella*, *Shigella*, and *Pseudomonas*) and a corresponding reduction in beneficial ones (lactobacilli and bifidobacteria).²¹ In an analysis of data on patients with diarrhea-, constipation-, or mixed-symptom type IBS, treatment with *Lactobacillus* was beneficial in both adult and pediatric patients (odds ratio [OR] 17.62, 95% CI 5.12–60.65 and OR 3.71, 95% CI 1.05–13.11, respectively).²² A meta-analysis of results reported in 23 trials comprising 2575 subjects who received either single strains or a combination showed a beneficial effect of probiotics on global IBS symptom, abdominal pain, bloating, and flatulence scores, with an RR of symptom persistence with probiotics compared with placebo of 0.79 (95% CI 0.70–0.89).²³ These findings have been supported in a more recent meta-analysis.²⁴ Prebiotics also have been assessed in a meta-analysis and have been found not to relieve GI symptoms or improve quality of life in patients with IBS.²⁵ According to the American College of Gastroenterology monograph on the subject, prebiotics are not recommended for IBS owing to insufficient evidence.²⁶

Hepatic Disorders

In the presence of alcoholic liver disease, consumption of alcohol causes alterations in gut microbiota composition, resulting in endotoxemia and worsening hepatic function.²⁷ The use of probiotics such as VSL#3, *Lactobacillus* spp., *E. coli* Nissle, and *B. bifidum* is associated with reductions in liver function test abnormalities and improvement in Child-Pugh scores (assessing severity of liver disease) and in MELD (model for end-stage liver disease) scores. In a study in patients with cirrhosis, use of VSL#3 showed a reduction in hospitalization necessitated by hepatic encephalopathy.²⁸ Reduced risk of hepatic encephalopathy with probiotic use also was supported by a meta-analysis (OR 0.42, 95% CI 0.26–0.70); however, mortality rate and serum ammonia concentrations were not affected (OR 0.73, 95% CI 0.38–1.41; weighted mean difference [WMD] –3.67, 95% CI –15.71 to 8.37, respectively).²⁹ The beneficial effects of probiotics may not be limited to alcoholic liver disease: A meta-analysis of data on nonalcoholic fatty liver disease (NAFLD) showed

similar reductions in the transferase enzymes aspartate transaminase (AST) and alanine transaminase (ALT) (respective mean differences of -19.77 , with 95% CI -32.55 to -7.00 , and -23.71 , with 95% CI -33.46 to -13.95).³⁰ The prebiotic lactulose is a mainstay of therapy for hepatic encephalopathy, which is available by prescription rather than over the counter; this clinical scenario is beyond the scope of this chapter.³¹ A recent meta-analysis also has shown benefit of prebiotics and probiotics for reducing infections after hepatic resection.³²

***Clostridioides difficile* Infection**

Antimicrobials disrupt the normal function and composition of the intestinal microbiota. This disturbance enables colonization by *Clostridioides difficile*, an anaerobic, gram-positive, spore-forming bacillus. Its etiopathogenetic mechanism is production of toxin, which causes inflammation and diarrhea.

Some evidence suggests that probiotics may be useful in the primary prevention of *C. difficile* infection (CDI) when administered concurrently with antimicrobials. A meta-analysis of 23 trials comprising 4213 subjects compared probiotics and placebo for the primary prevention of CDI.³³ CDI occurred in 2.0% of the probiotics group, compared with 5.5% of the control group (RR 0.36, 95% CI 0.26–0.51). The results were similar in comparisons of adult and pediatric subjects, lower and higher doses, and different probiotic species. Subjects in the probiotics group experienced lower rates of abdominal cramping, nausea, fever, soft stools, flatulence, and taste disturbance (RR 0.80, 95% CI 0.68–0.95). In many of the trials, the probiotic regimen was started within 3 days of initiation of antibiotics and continued for at least the entire duration of antibiotic treatment.³⁴

Overall, however, according to CDI-specific guidelines from the Society for Healthcare Epidemiology of America, the Infectious Diseases Society of America, and the American College of Gastroenterology, the evidence is insufficient to recommend administering probiotics for primary prevention of CDI.³⁵ As reported in the most recent literature, recommendations have been published for the use of Bio-K+, a product approved in Canada, containing 50 billion CFUs of *L. acidophilus* CL1285 and *L. casei* LBC80R to prevent nosocomial CDI in hospitalized patients.³⁶ As the older guidelines are updated, further recommendations on use of probiotics to prevent CDI may become available. To date, relevant data are limited, and no specific recommendation

regarding probiotics for the treatment of CDI or prevention of recurrence has been issued.^{35,36}

Antibiotic-Associated Diarrhea

Diarrheal disease is a common adverse effect of antibiotics and is referred to as antibiotic-associated diarrhea (AAD). AAD is due to a disruption of normal intestinal microbiota. Concomitant probiotic use may mitigate this disruption. In a pooled analysis of data for 4097 adult and pediatric subjects from 25 trials, probiotics reduced the incidence of AAD (RR 0.60, 95% CI 0.49–0.72).³³ Similarly, in an analysis of 22 trials comprising 4155 pediatric patients, probiotics reduced the incidence of AAD (RR 0.42, 95% CI 0.33–0.53).³⁷ No significant effect by type of antibiotic or by dose of probiotic (greater than or less than 10¹⁰ CFU/day) was observed. Neither of these analyses reported results for use of a specific probiotic; rather, the results are based on various probiotic regimens. The use of probiotics with antibiotics may be of benefit, but a specific strain cannot be recommended.

Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) involves bowel wall necrosis and potential bowel wall perforation, especially in preterm infants of low birth weight, and is associated with increased mortality.³⁸ Probiotics may be beneficial in reducing the complications of NEC. In a meta-analysis of randomized, controlled trials in preterm infants (born at less than 37 weeks of gestation or weight less than 2500 g, or both), the use of probiotics for more than 7 days significantly reduced the incidence of severe NEC (RR 0.43, 95% CI 0.33–0.56 for 20 studies with 5529 infants) and mortality (RR 0.65, 95% CI 0.52–0.81 for 17 studies with 5112 infants).³⁸ Probiotics did not affect the development of sepsis (RR 0.91, 95% CI 0.80–1.03 for 19 studies with 5338 infants).

In a subgroup analysis based on the type of probiotic evaluated, *Lactobacillus* species or a mixture of two or three probiotic species significantly reduced the incidence of severe NEC (RR 0.45, 95% CI 0.27–0.75 for five studies with 1955 infants and RR 0.37, 95% CI 0.25–0.54 for nine studies with 2807 infants), whereas change in incidence with *Bifidobacterium* species and *Saccharomyces boulardii* did not reach significance (RR 0.48, 95% CI 0.16–1.47 and RR 0.72, 95% CI 0.34–1.55, respectively); however, these strains were evaluated in fewer subjects (409 and 357, respectively), which may have limited

the power of the analyses.³⁸ Another meta-analysis reported similar findings based on 12 cohort studies comprising 10,800 premature infants.³⁹ The use of probiotics was associated with a reduction in occurrence of NEC (RR 0.55, 95% CI 0.39–0.78) and death (RR 0.72, 95% CI 0.61–0.85) but did not affect sepsis rates (RR 0.86, 95% CI 0.74–1.00). The use of probiotics in preterm infants appears to prevent severe NEC and to reduce all-cause mortality rates. *Lactobacillus* species or mixtures of probiotics were most effective, but more studies are needed to determine the efficacy of other strains, as well as optimal dose and duration. Two recent systematic reviews and meta-analyses assessed use of probiotic therapy with *Bifidobacterium* species and found that these strains were effective and safe for preventing NEC in preterm infants.^{40,41}

***Helicobacter pylori* Infection**

Helicobacter pylori is an infective organism that colonizes the upper GI tract, causing peptic ulcer disease in susceptible patients. *H. pylori* also is a known carcinogen, so patients who test positive for *H. pylori* infection require treatment for eradication of the pathogen. Combination therapy with an antisecretory agent such as a proton pump inhibitor, plus a combination of antibiotics and potentially bismuth, for 7–14 days is currently recommended.⁴² Increasing antimicrobial resistance rates and adverse effects related to combination therapy affect eradication rates and patient tolerance of these regimens. The use of probiotics may increase eradication rates and reduce the occurrence of adverse effects.

A meta-analysis of 45 randomized controlled trials and 6997 participants showed higher rates of *H. pylori* eradication with 7 days of triple therapy (one proton pump inhibitor and two antibiotics) plus probiotics compared with triple therapy alone (82.31% versus 72.08%, respectively; eradication RR 1.11, 95% CI 1.08–1.15).⁴³ Additionally, the rate of adverse effects was much lower with probiotics plus triple therapy than with triple therapy alone (21.44% versus 36.27%, respectively; RR 0.59, 95% CI 0.48–0.71). Although eradication rates were higher, with fewer adverse effects, the addition of probiotics to triple therapy did not have an effect on patient compliance (RR 0.98, 95% CI 0.68–1.39). This may be due in part to the short duration of therapy. These findings are consistent with those of another meta-analysis, which evaluated 11 studies with 2392 participants.⁴⁴ The eradication rates were reported as 83% for 7 days of triple therapy plus probiotics and 73% for 7 days of triple therapy (RR 1.14, 95% CI 1.07–1.20). Adverse effects also were similar to those in the

foregoing analysis (RR 0.65, 95% CI 0.47–0.87). This analysis also evaluated subgroups based on probiotic strain used. Eradication rates were significant for a number of probiotic strains including *Lactobacillus*, *Bifidobacterium*, *Streptococcus*, and *Saccharomyces*. It would be reasonable to consider the addition of probiotics to standard therapy for the duration of the treatment course. The current *H. pylori* treatment guidelines recognize the potential value of probiotics for adjuvant therapy. However, limited evidence precludes recommending their use for the treatment of *H. pylori* infection at present.⁴²

Diabetes Mellitus

Probiotics have been evaluated for the treatment of diabetes. It has been proposed that probiotics reduce inflammation and prevent pancreatic beta cell destruction, resulting in a reduction of blood glucose.⁴⁵ In a meta-analysis of eight trials comprising 429 subjects, the probiotics users experienced a significant reduction in fasting plasma glucose (FPG) compared with subjects in the control groups (change in FPG –15.92 mg/dL, 95% CI –29.75 to –2.09).⁴⁵ HbA_{1c} (glycated hemoglobin) also was significantly reduced in the probiotics group in a subgroup analysis of three trials comprising 158 subjects (HbA_{1c} reduction 0.54%, 95% CI 0.82–0.25). The use of preparations with multiple strains of probiotics maintained a significant reduction in FPG, whereas the use of single-strain preparations did not (FPG weighted mean difference [WMD] with multiple strains –35.41 mg/dL, 95% CI –51.93 to –18.48; FPG WMD with single strains 2.67 mg/dL, 95% CI –18.78 to 24.13). Additionally, the use of probiotics for 8 weeks resulted in a reduction in FPG, whereas shorter durations of therapy did not (FPG WMD for 8 weeks –20.34 mg/dL, 95% CI –35.92 to –4.76; FPG WMD for <8 weeks –14.29, 95% CI –65.83 to 37.26). These results concur with those for a previous meta-analysis, which reported similar reductions in FPG in subjects receiving probiotics compared with the control subjects.⁴⁶

Cardiovascular Risk Factors

Probiotics may play a role in management of cardiovascular disease by affecting lipid levels. It has been hypothesized that probiotics may assimilate cholesterol during growth, bind cholesterol, disrupt cholesterol micelles, and deconjugate bile salts.⁴⁷ In a meta-analysis of 13 trials comprising 485 subjects that evaluated probiotics' effects on cholesterol in patients with normal, borderline high, and high cholesterol levels, probiotics significantly reduced

total blood cholesterol (mean net change -6.40 mg/dL; 95% CI -9.93 to -2.87).⁴⁸ Low-density lipoprotein (LDL) cholesterol also was significantly reduced in the probiotics group (mean net change -4.90 mg/dL, 95% CI -7.91 to -1.90). Two other recent meta-analyses corroborate these findings.^{47,49} Although probiotics significantly decreased total cholesterol and LDL, these meta-analyses did not address clinical outcomes. Also, the trials included in the analyses were of short duration, with the longest trial lasting 10 weeks.

Probiotics may have an effect on other cardiovascular risk factors. A meta-analysis of four studies comprising 234 subjects reported a significant reduction in body mass index (BMI) with use of probiotics (-0.52 kg/m², 95% CI -0.80 to -0.24 kg/m²).⁴⁹ It also found that waist circumference decreased significantly with probiotic use in 304 subjects across four studies (mean decrease -2.11 cm, 95% CI -3.54 to -0.68 cm).

Probiotics also have been evaluated in the management of hypertension. Data are limited, but modest reduction in blood pressure was demonstrated in one meta-analysis of data for patients with hypertension who received probiotic supplementation.⁵⁰

Eczema and Dermatitis

Development of eczema was shown to be less likely in infants who were exposed to probiotics—either through the pregnant mother’s receiving probiotics during the third trimester, the mother’s receiving probiotics while breastfeeding, or the infant’s receiving probiotics after birth, or some combination of these—was less likely than in infants without probiotic exposure. Probiotics did not reduce the incidence of other types of allergic diseases in infants in this analysis.⁵¹

Probiotic use by pregnant mothers or some form of exposure in infants up to 6 months of age was found to significantly reduce the incidence of eczema in in these infants in a meta-analysis of data for 2797 subjects (RR 0.74, 95% CI 0.67–0.82).⁵²

Atopic Dermatitis

In a meta-analysis evaluating use of probiotics for the primary prevention of atopic dermatitis (AD), supplementation with probiotics based on 16 studies was protective against the development of AD (OR 0.64, 95% CI 0.56–0.74).⁵³ In

subgroup analyses, the protective effects of probiotics were maintained in the general population, as well as in subjects who were at high risk for development of allergies. Administration of prenatal plus postnatal probiotics was effective, whereas administration of probiotics only in the prenatal or the postnatal period was not. The results did not differ with the probiotic strain used. On the basis of this analysis, probiotics seem to be beneficial for AD prevention if they are administered during the pre- and postnatal periods in both the general population and in those at risk for allergy. These findings are supported by another meta-analysis.⁵⁴ Additionally, a meta-analysis of 14 studies evaluated the effects of probiotic supplementation during pregnancy or in infancy on the development of AD.⁵⁵ Among the subjects who received probiotics, the development of AD was less likely than in those in control groups (RR 0.79, 95% CI 0.71–0.88). The benefit of probiotics was essentially the same whether they were administered during only during pregnancy or during pregnancy and also in infancy.

Probiotics also have been evaluated in the treatment of AD.⁵⁶ A meta-analysis included 25 randomized controlled trials comprising a total of 1599 subjects and reported a significant improvement in the standardized SCORAD (SCORing Atopic Dermatitis) value for all subjects receiving probiotics compared with placebo (WMD –4.51, 95% CI –6.78 to –2.24). Probiotics' beneficial effects were seen in two of three age-related subgroups: in children 1 to 18 years of age (WMD –5.74, 95% CI –7.27 to –4.20) and in adults (WMD –8.26, 95% CI –13.28 to –3.25). The benefit was not seen in infants younger than 1 year (WMD 0.52, 95% CI –1.59 to 2.63).

For atopy and dermatitis, *Lactobacillus rhamnosus* GG is the most researched and most often recommended, although *L. acidophilus* and *Bifidobacterium lactis* also have been shown to be of benefit.^{57,58} Lactobacilli and bifidobacteria are dosed at 1–10 billion CFU per day, given in divided doses. *S. boulardii* is dosed at 250–500 mg 2–4 times daily.

Respiratory Syndromes

Probiotics have been assessed in the treatment of allergic rhinitis: An analysis of 23 studies (1919 subjects) showed that probiotics improved Rhinitis Quality of Life (RQLQ) scores compared with placebo (standard mean difference [SMD] –2.23, 95% CI –4.07 to –0.4).⁵⁹ The RQLQ is a 7-point scale, with lower scores indicating better quality of life. A change of 0.5 point is considered to be a

minimally important difference; a change of 2 or more points represents a substantial effect.⁶⁰ In a recent meta-analysis of data for *Lactobacillus paracasei* versus placebo, probiotics were effective in reducing nasal and ocular symptom scores and total nasal and ocular quality of life scores.⁶¹

Probiotics also may be of benefit in the setting of upper respiratory tract infections (URIs). In a meta-analysis of 12 trials comprising 3720 subjects of different ages, ranging from children to older adults, use of probiotics was associated with a lower risk for development of a URI compared with placebo (OR for development of one URI 0.53, 95% CI 0.37–0.76, OR for development of at least three episodes 0.53, 95% CI 0.36–0.8).⁶² Probiotic therapy also had positive effects on the mean duration of URI episodes (mean difference –1.89 days, 95% CI –2.03 to –1.75), rate of antibiotic prescriptions (OR 0.65, 95% CI 0.45–0.94), and common cold–related school absences (OR 0.10, 95% CI 0.02–0.47). Adverse effects were similar for the probiotics and placebo groups (OR 0.88, 95% CI 0.65–1.19), with the most common adverse effects reported as minor gastrointestinal disturbances. Similar findings were reported in an analysis of 11 studies comprising 2417 pediatric subjects younger than 10 years of age.⁶³ A later meta-analysis showed that *Lactobacillus rhamnosus* (formerly thought to be a subspecies of *L. casei*) was the only probiotic to reduce the incidence of respiratory tract infections compared with placebo.⁶⁴

Assessment of Safe Use of Probiotics

Probiotics may be associated with minor GI adverse effects including cramping, nausea, soft stools, flatulence, and taste disturbance.⁶⁵ However, it has been reported that patients who receive probiotics to treat CDI are less likely to experience GI adverse effects than patients who are not treated with probiotics. Additionally, it often is difficult to determine whether these GI effects are due to the administered probiotic or to the underlying GI disease state being treated.

A concern with the use of probiotic therapy is the development of systemic infection with organisms in the live culture being administered. In a number of case reports, immunocompromised patients have acquired serious infections (e.g., sepsis, endocarditis, fungemia) with infectious organisms consistent with the administered probiotic.⁶⁵ Even though probiotic administration has become more common, an increase in infection risk has not been supported

by population-based data of the rates of infections due to commonly administered probiotic strains. Although some data support the use of probiotics in immunocompromised patients, such products should be avoided in this population because of reports of associated systemic infection.⁶⁶

A multicenter randomized, double-blind, placebo-controlled study called the Probiotics in Pancreatitis Trial (PROPATRIA) assessed the effects of probiotics for the prevention of infectious complications in patients with predicted severe acute pancreatitis.⁶⁷ This trial demonstrated that probiotics had no effect on the rate of infectious complications. However, the mortality rate was more than doubled in the probiotics group, with a relative risk of 2.53 (95% CI 1.22–5.25). Bowel ischemia and associated mortality were significantly higher in the probiotic group ($P = 0.004$). Therefore, probiotics should be avoided in such at-risk patients. By contrast, no harmful effects have been observed in women in late-stage pregnancy or in breast-feeding infants during long-term use.⁶⁸ Additionally, providing probiotics via a jejunostomy tube has been reported to potentially increase risk of adverse effects. This association may be due to the lack of contact of the probiotics with gastric acid, resulting in increased exposure of the GI tract to viable probiotic organisms.⁶⁹

Cases 20–1 and 20–2 illustrate two different situations in which probiotics are useful and detail how both potential safety and efficacy should be evaluated.

Case 20–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient reports severe epigastric pain, especially at night and after eating a spicy or fried meal. Over-the-counter antacids seem to reduce the pain, but it recurs soon after. She also complains of pain with swallowing (dysphagia) and sometimes has difficulty swallowing (odynophagia). She

	underwent esophagogastroduodenoscopy (EGD) and was found to be positive for <i>Helicobacter pylori</i> infection.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Her symptoms worsen when she eats spicy or fried foods, or when she is under a lot of stress at work.
c. Description of the patient's efforts to relieve the symptoms	The patient has been taking Tums or Mylanta as needed to relieve her symptoms.
d. Patient's identity	Mary Carpenter
e. Patient's age, gender, height, and weight	52 years, female, 5 ft 2 in., 130 lb (59 kg)
f. Patient's occupation	Air traffic controller
g. Patient's dietary habits	Does not cook for herself; relies on prepared foods or takeout from fast food restaurants for most of her meals.
h. Patient's sleep habits	6 hours per night
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	She is having a prescription filled today for clarithromycin 500 mg bid, amoxicillin 1 g bid, and omeprazole 20 mg bid for 10 days. She will discontinue taking Tums and Mylanta with initiation of her <i>H. pylori</i> antibiotic/acid suppression regimen.
j. Allergies	NKDA
k. History of other adverse reactions to medications	None
l. Other (describe) _____	None
Assess	
2. Differentiate patient's signs/symptoms and correctly identify the patient's primary problem(s).	Ms. Carpenter has been diagnosed with <i>H. pylori</i> infection, for which appropriate treatment with triple therapy has been prescribed.
3. Identify exclusions for self-treatment.	None

4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer Ms. Carpenter to an appropriate health care provider. (2) Recommend self-care with a probiotic. (3) Recommend stress reduction through activities such as yoga or meditation. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Ms. Carpenter may consider adding a probiotic to her <i>H. pylori</i> regimen such as <i>Lactobacillus rhamnosus</i> GG: 6×10^9 CFU twice daily for 10 days.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Probiotics taken in combination with an <i>H. pylori</i> eradication regimen have been shown to increase its effectiveness and to reduce any adverse effects of the drugs in this regimen (such as diarrhea)."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Probiotics are a good option for you because they treat the specific symptoms you are experiencing."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
Solicit follow-up questions from the patient or caregiver.	"Will I get an infection from taking a probiotic since you told me this is a live microorganism?"
Answer the patient's or	"In patients like you with a healthy immune system,

caregiver's questions.	probiotics are safe to use and won't cause an infection. They are not recommended for patients with weakened immune systems such as those receiving chemotherapy or who have had organ transplant."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Ask Ms. Carpenter to call to update you on her response to your recommendations. Alternatively, you could call her in 1 week to evaluate how she is progressing and tolerating therapy.

Key: CFU = Colony-forming units; NDKA = no known drug allergies.

Case 20-2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient complains of new-onset cramping abdominal pain, which started 6 weeks ago. He also reports passage of 2-3 bloody loose stools per day.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	His symptoms worsened when he recently quit smoking.
c. Description of the patient's efforts to relieve the symptoms	The patient tried loperamide for his diarrhea without any relief.
d. Patient's identity	Harry Smith

e. Patient's age, gender, height, and weight	40 years, male, 5 ft 10 in., 190 lb (86.4 kg)
f. Patient's occupation	Engineer
g. Patient's dietary habits	Mr. Smith generally eats a well-balanced diet.
h. Patient's sleep habits	5-6 hours nightly
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	None
j. Allergies	None
k. History of other adverse reactions to medications	None
l. Other (describe) _____	None
Assess	
2. Differentiate patient's signs/symptoms and correctly identify the patient's primary problem(s).	Mr. Smith's signs and symptoms include new-onset cramping abdominal pain and passage of 2-3 bloody loose stools per day.
3. Identify exclusions for self-treatment.	Mr. Smith has blood in his stool, which warrants referral for more invasive testing such as with colonoscopy. This specific finding is an exclusion for self-treatment.
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer the patient to an appropriate health care provider. (2) Recommend self-care with a probiotic and nonprescription antidiarrheal medication. (3) Recommend self-care until

	the patient can see an appropriate health care provider. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Refer Mr. Smith to an appropriate health care provider.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"You should consult a health care provider for treatment."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Your symptoms of blood in the stool require further evaluation. Once a diagnosis is made, we can recommend further appropriate therapies."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	Criterion does not apply in this case.
Solicit follow-up questions from the patient or caregiver.	Criterion does not apply in this case.
Answer the patient's or caregiver's questions.	Criterion does not apply in this case.
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Mr. Smith in 1–2 days to ensure that he made an appointment to seek medical care.

Patient Counseling

Many probiotic preparations with one or multiple species and wide dosing

ranges are available. Health care providers and consumers should be thoughtful when selecting probiotic formulations and should base this decision on clinical trial data and the strains used in these trials. Patients should be counseled to avoid probiotics if they have risk factors for systemic infections or other complications.⁶⁵ This high-risk group includes persons with valvular heart disease, premature infants, patients with central venous access ports, and immunocompromised patients.

Product quality has been a concern because some studies found products containing few or no live cultures; refrigerated products have been recommended as perhaps less likely to have suffered from degrading temperatures.⁷⁰ However, recent research suggests that nonviable probiotics also may offer benefit.⁷¹

Key Points for Prebiotic and Probiotic Use

- Prebiotics are substrates that are selectively utilized by host microorganisms in processes that support gut health and include fermentable dietary components that selectively stimulate the growth and/or activity of one or a limited number of bacterial strains in the colon (bifidobacteria and lactobacilli), thereby benefiting the host.
- Probiotics are nonpathogenic, living microorganisms that have beneficial health effects when consumed regularly in adequate amounts. They often are present in fermented products from milk (yogurt and kefir) or plants (sauerkraut and miso).
- Probiotics have shown beneficial effects in a number of diseases; however, the particular species and strain and the dose necessary for beneficial effects often remain controversial and may vary from condition to condition.

Chapter 21: Poisoning

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Poisoning is the leading cause of injury-related death in the United States, surpassing motor vehicle crashes and firearms injuries in this etiologic category. As such, it constitutes a major public health problem.^{1,2} Drug-related morbidity also is significant.

Use of nonprescription medications carries a risk for adverse effects and poisoning in all age groups, but especially in persons at the extremes of age. Health literacy, level of cognitive function, visual acuity, and personal knowledge base, attitudes, and beliefs are factors that may influence how people take a nonprescription medication and therefore their risk for adverse effects.³ Consumers often are unaware of ingredients in combination nonprescription products, particularly pain relief and upper respiratory tract products.⁴ Studies of patient perceptions of nonsteroidal anti-inflammatory drugs (NSAIDs), with their associated risks and specific indications, have found general understanding to be relatively poor, potentially resulting in inappropriate use, dosing that exceeds daily limits, or concomitant self-administration of several different NSAIDs.^{5,6} Restrictions and label changes on pediatric cough and cold preparations have led to a reduction in pediatric unintentional poison exposures and hospital emergency department visits.^{7,8}

Acetaminophen is one of the leading nonprescription pain relievers. Misuse of acetaminophen also is a major cause of poisoning, both unintentional and intentional, reported to U.S. poison control centers. The Acetaminophen Awareness Coalition, whose members include the American Pharmacists Association, the National Association of Boards of Pharmacy, and the National Community Pharmacists Association, launched a website (www.knowyourdose.org) to educate patients and consumers about how to use acetaminophen correctly. Initiatives to promote safe use of this drug include converting pediatric liquid acetaminophen preparations to one standardized concentration and highlighting the ingredient acetaminophen on nonprescription labels. Most poisonings in young children are unintentional, whereas poisonings in other age groups may be unintentional or intentional (e.g., with suicide attempts or medication misuse). Use of nonprescription cough and cold medications for their psychoactive effects, to obtain a pharmaceutical “high,” remains an issue identified through the

Monitoring the Future study, with 3.2% of 12th graders indicating use of these medications in the past year.⁹ A majority of poisonings are a result of ingestion of a substance, but poisonings also may occur after a toxin is inhaled or comes into contact with the skin and eyes. Bites and envenomations are other potential sources of toxin exposures. First aid for poisonings focuses on minimizing the extent of the exposure and stemming the progression or development of toxicity.

Poison control centers are 24-hour resources for poison information, clinical toxicology consultation, and poison prevention education. They are staffed around the clock with pharmacists, nurses, physicians, and physician assistants who have additional training in clinical toxicology. The centers are available for consultation to both health care providers and the public. The entire United States and its territories are covered by a network of poison control centers. An area-specific poison control center should always be contacted for assessment and treatment of poisonings; these centers also constitute an excellent source of educational materials on poisoning prevention. [Figure 21-1](#) shows the nationwide poison control center number and logo.



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Figure 21–1 Nationwide toll-free telephone number for contacting a poison control center. (Source: Reprinted with permission from the American Association of Poison Control Centers, Alexandria, Virginia.)

In 2018, a total of 55 poison control centers serving the United States and territories reported 2,099,751 cases to the National Poison Data System of the American Association of Poison Control Centers.¹⁰ A majority of poison exposures (44.17%) occur in children younger than 6 years, of which 73.7% involve children younger than 3 years of age.¹⁰ Nonprescription and prescription medications are frequently responsible for potentially toxic exposures reported to poison control centers. Nonprescription products such as analgesics, dietary supplements, topical preparations, vitamins, and antihistamines are among the most common substances ingested by young children. The large number of nonprescription medications involved in pediatric exposures reflects the common use and availability of these products in the home. Other common substances and items involved in potential poison exposures in children younger than 6 years include cosmetics and personal care products, cleaning substances, foreign bodies or toys, pesticides, and plants.

A majority (65.6%) of poison exposures reported to poison control centers are managed at the site of the exposure, usually in a residence; only 12.5% of children younger than 6 years are managed in a health care facility. Major effects or fatal outcomes were reported in 1.5% of cases recorded for 2017.¹⁰ Consultations with poison control centers are cost-effective, with a favorable cost-to-benefit ratio.¹¹ A significant portion of the cost savings results from home observation, as well as from the reduction in unnecessary emergency medical transport and treatment costs. A policy analysis group showed that poison center consultations resulted in improved outcomes and a reduction in length of stay by 0.43 day among Medicare beneficiaries.¹² The same group previously reviewed the existing literature on the cost savings associated with use of a poison control center and estimated medical care savings and reduced productivity loss of \$13.39 per year per dollar of poison control center funding.¹³ Health care providers are encouraged to work closely with their local poison control centers to ensure the most appropriate, cost-effective care for the poisoned patient.

Consumers and/or health care providers also can use an online/smart phone app to assist them in deciding whether to call their poison control center. For those who prefer this approach, such tools can be useful and cost-effective. [WebPoisonControl.org](https://www.webpoisoncontrol.org) is a free application that was launched in December 2014. In 1 year, more than 9000 public cases have been logged, and in 73.3% of these cases, self-treatment for poisoning events at home was determined to be safe with the appropriate precautions.¹⁴ In 24.5% of the cases, the user was referred to a poison control center, and in 2.1% of cases, the user was referred directly to a hospital emergency department. A survey of users demonstrated that more than 91% thought the tool was quick and easy to use. Another online resource launched in 2017 is poisonhelp.org. Other online/smart phone apps may be available in the near future.

Unintentional childhood poisonings remain a common cause of injury-related morbidity, requiring significant expenditures of health care dollars for inpatient and outpatient care. Unintentional poisonings remain one of the leading causes of injury-related hospitalizations in preschool children; however, fatalities among preschoolers have declined significantly since the early 1970s. According to an analysis of the National Electronic Injury Surveillance System–All Injury Program (NEISS–AIP), an estimated 58,000 children younger than 6 years are evaluated in emergency departments annually for unintentional medication-related exposures.¹⁵ Hospitalization or

specialized medical care was required in nearly 16% of cases. The most common categories of medications were acetaminophen, cough and cold medications, antidepressants, and NSAIDs.

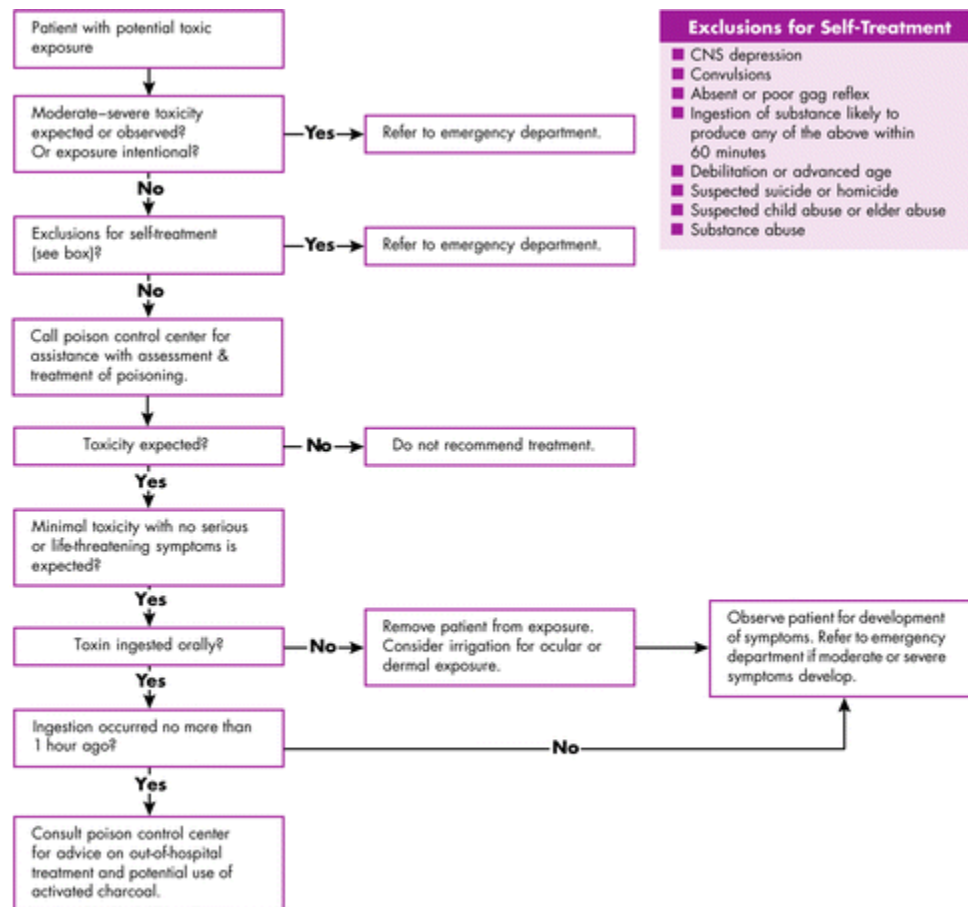
The National Safety Council reported 38 deaths caused by unintentional poisoning in children younger than 5 years in 2017.¹⁶ Only 25 of the 3208 fatalities reported by poison control centers in 2017 involved children younger than 6 years.¹⁰ Medications and illicit drugs (excluding ethanol) were the primary substances responsible for fatalities involving persons of all ages. Child-resistant closures (CRCs) legislated through the Poison Prevention Packaging Act (PPPA) of 1970 help prevent unintentional poisonings. Incorporating CRCs into packaging has been responsible for a decline in pediatric fatalities from both prescription and nonprescription medications.¹⁷ Although CRCs have improved child safety, exemptions to the law allow dispensing medications without CRCs.¹⁸ An analysis of NEISS data revealed that an estimated 55% of nonfatal poisonings in children younger than 5 years treated in an emergency department involved a product regulated by the PPPA.¹⁹ Whereas CRCs may reduce unintentional pediatric poisoning, use of nonstandard liquid measuring devices and caregiver misinterpretation of nonprescription medication labels are recognized to increase the risk for pediatric poisoning. Further work is needed to improve the format and content of nonprescription labels to optimize caregiver understanding of the medication and dosing instructions.^{3–6}

Clinical Presentation of Poisoning

Poisons can affect every organ system. Signs and symptoms of poisoning can range in severity from mild to life-threatening. For some drugs, manifestations of toxicity after overdose are similar to adverse effects associated with therapeutic use. For example, ibuprofen overdose is characterized primarily by nausea, vomiting, and abdominal pain. Patients with diphenhydramine overdose may exhibit sedation or stimulation (e.g., agitation, hallucinations), tachycardia, hypertension, dry mouth, and dilated pupils from the drug's antimuscarinic properties. Overdoses of other drugs, such as aspirin, result in multiorgan system effects, including gastrointestinal (GI), central nervous system, metabolic, cardiovascular, pulmonary, and hematologic toxicity. A lack of symptoms immediately after a poison exposure does not preclude toxicity. Patients may be asymptomatic initially, but severe toxicity may develop hours

after ingestion of some sustained-release or enteric-coated products or of medications that delay gastric emptying or slow GI motility (e.g., antihistamines). For other drugs (e.g., acetaminophen) and some chemicals (e.g., methanol, acetonitrile), clinical effects are delayed while the substance is metabolized to active or toxic metabolites. The time course of acetaminophen overdose is related to formation and covalent binding of a toxic metabolite to hepatic cells. As a result, a relatively mild initial clinical course characterized by nausea, vomiting, anorexia, and malaise can be followed by onset of severe hepatic and renal toxicity 3–5 days later. An important consideration in any setting is that symptoms may be due to causes other than poisoning. If symptoms are serious, they warrant medical attention.

Algorithm: Poisoning



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Figure 21–2 Self-care for poisoning. Key: CNS = Central nervous system.

Treatment of Poisoning

Most unintentional poison exposures in small children result in minimal, if any, adverse effects and require no treatment, and observation is a sufficient approach to management. Although self-treatment may be appropriate, health care providers, caregivers, and patients are encouraged to seek advice from the nearest poison control center before attempting any treatment.

Treatment Goals

The primary goal of at-home or prehospital therapy is to prevent absorption of toxins or stem the progression of toxicity, thereby minimizing morbidity and mortality risks.

General Treatment Approach

The first step in assessing a potential poison exposure is to determine whether the patient has symptoms and whether the exposure puts the patient at risk for toxicity. Many exposures are, in fact, nontoxic or minimally toxic, because either the substance has very low inherent toxicity or the amount consumed is too low to cause toxicity. A decision regarding the option for self-treatment depends on the reason or circumstance of the poison exposure, toxicity of the agent, and general health status of the patient. Self-treatment should be considered only if the ingestion is unintentional and the potential for toxicity is assessed as minor. With any inadvertent exposure to a toxin that potentially can result in moderate to severe toxicity, as well as all intentional exposures, the patient should be referred immediately to a hospital. If the patient exhibits potentially life-threatening clinical effects (e.g., coma, convulsions, syncope), transportation to a hospital emergency department should be arranged immediately through the emergency 911 system. Additional exclusions for self-treatment can be found in [Figure 21–2](#). Hospital care includes observing the patient, supporting vital functions (e.g., airway, breathing, circulation), preventing absorption, enhancing elimination, and using available antidotes.

Suicide is a serious public health problem in the United States. Intentional ingestions of medications often represent a cry for help. Persons who are trying to harm themselves or are abusing or misusing drugs on purpose are

not always truthful about what they ingested. It is important to be vigilant and recognize when a patient has taken a medication purposefully and to refer the person immediately for evaluation in an emergency department.

A majority of patients who do not require immediate hospital referral are managed with on-site observation only, with no specific treatment.¹⁰ In some instances, the optimal approach is to attenuate the exposure by irrigation or prevention of further absorption. The nonprescription product activated charcoal may prevent or reduce the absorption of some ingested substances. However, its routine use is not recommended without consultation with a poison control center. [Figure 21–2](#) outlines self-care for exposure to poisons.

Nonpharmacologic Therapy

Inhalation exposures are managed by removing the patient from the toxic fumes to fresh air. Irrigation may be beneficial to decrease the contact time of a chemical with skin or mucosal surfaces. Exposed skin should be washed with soap and water (usually twice) to decrease the contact time with the offending chemical, with care taken to include nail beds and hair when appropriate. Irrigation of the eye with water should be initiated immediately after an ocular exposure to a chemical or drug not intended for ocular use (e.g., inadvertent ocular administration of an otic preparation). If an irritating chemical has been swallowed, administration of a small amount of fluids may decrease the contact time of the chemical with the mucosal surface. Neutralization after a chemical contacts skin or eyes or for ingested substances is not recommended.

Administration of oral fluids after ingestion of a drug is not usually recommended. Giving a large amount of fluids should be discouraged, because with a full stomach, spontaneous vomiting is more likely, which can be risky in some situations. The fluids theoretically may facilitate dissolution of a solid dosage form, thereby enhancing its absorption. Administering fluids after toxic ingestions should be considered for drugs recognized to be associated with a high risk of esophageal impaction, such as bisphosphonates, or those that may cause renal injury owing to dehydration, such as ibuprofen or other NSAIDs. Manually stimulating the gag reflex at the back of the throat with either a blunt object or a finger may induce vomiting, but this practice is not recommended because it can lead to soft palate injury.

Pharmacologic Therapy

Activated charcoal, an adsorbent, and ipecac syrup, an emetic, are the only approved agents for self-treatment for ingested poisons. Ipecac syrup does not improve outcomes for poisoned patients, however, and its use should be avoided.²⁰ Although the Code of Federal Regulations still states that ipecac syrup is considered the emetic of choice for certain poisoning scenarios, the American Academy of Pediatrics stopped recommending its use for poison treatment in 2003.²¹ Pharmacists should recommend discarding any existing supplies in the home. Controversy surrounds the use of activated charcoal as a self-treatment, in view of the lack of evidence that it improves outcome and its poor tolerability. Pharmacists should encourage consultation with a poison control center regarding first aid recommendations for poisoning.

Treatment With Activated Charcoal

Activated charcoal is a tasteless, gritty, fine, black insoluble powder made by pyrolysis of various organic materials.²² Its large surface area of 950–2000 m²/g makes activated charcoal a highly effective adsorbent.²²

Activated charcoal has been shown to be an effective adsorbent for a large number of commonly ingested drugs and many other toxic agents. These substances are bound in the internal surface of the pores of the charcoal particle, thereby preventing their absorption. Activated charcoal is not absorbed from the GI tract. As the ratio of activated charcoal to toxin increases, the proportion of bound toxin increases.²² Highly ionized substances, such as potassium and lithium, are poorly adsorbed by activated charcoal. Activated charcoal does not bind well to alcohols or glycols (e.g., ethanol, methanol, ethylene glycol), hydrocarbons, mineral acids and alkali, heavy metals (e.g., iron, lead, arsenic), or cyanide ([Table 21-1](#)). The presence of food in the GI tract may reduce the efficacy of activated charcoal.

Table 21-1 Contraindications to GI Decontamination With Activated Charcoal as Self-Treatment

Category	Inclusion Criteria	Recommendation
Patient condition	Coma, convulsions, syncope, airway or breathing problems, blood pressure or pulse irregularities, hallucinations, severe agitation; history of bariatric surgery	Refer to hospital for evaluation.

Category	Inclusion Criteria	Recommendation
Reason or circumstance	Intentional self-harm, substance abuse, malicious intent	Refer to hospital for medical and psychiatric or social service evaluation.
Ingestion of low-viscosity hydrocarbons and terpenes	Gasoline, kerosene, mineral seal oil (furniture polish), naphtha (lighter fluid), pine oil (cleaners), turpentine (paint removers), mineral oil	Contact poison control center.
Ingestion of caustic substances	Methacrylic acid (artificial nail primers), sodium silicate and carbonate (automatic dishwashing detergents), sulfuric acid (automotive battery, drain cleaners, toilet bowl cleaners), sodium hydroxide (drain cleaners, oven cleaners, hair relaxers), hypochlorites (bleach, pool chlorine), thioglycolates (hair relaxers), hydrofluoric acid (rust removers), hydrochloric acid (toilet bowl cleaner)	Contact poison control center.
Ingestion of substances not adsorbed by charcoal	Ethanol (alcoholic beverages, colognes, mouthwashes, aftershaves, hand sanitizers), isopropyl alcohol (rubbing alcohol), methanol (windshield washer fluid), ethylene glycol (antifreeze), ionized substances (potassium), metals (iron, lithium, lead, arsenic), cyanide (potassium cyanide, acetonitrile artificial nail remover, laetrile)	Contact poison control center.

Key: GI = Gastrointestinal.

Activated charcoal is approved by the U.S. Food and Drug Administration (FDA) for use as an emergency antidote for treatment of poison ingestion. Home administration of activated charcoal should never include more than 1 dose. The usual dose of activated charcoal is approximately 1 g/kg ([Table 21-2](#)).²² This dosage provides an estimate of the amount (rounded to the nearest full or half-full bottle) of activated charcoal to administer. Activated charcoal is available premixed either with water or with water and carboxymethylcellulose. Activated charcoal combined with sorbitol also is available to improve palatability and to act as a cathartic, shortening transit time of the activated charcoal complex through the GI tract and preventing constipation; however, most activated charcoal products marketed specifically

for home use do not contain sorbitol. Examples of nonprescription activated charcoal products are Actidose-Aqua and Liqui-Char with or without sorbitol; they generally are available at strengths of 15 g/72 mL, 25 g/120 mL, and 50 g/240 mL. Activated charcoal slurries are prone to settling, so they should be shaken vigorously before administration. Failure to shake the slurry adequately can result in delivery of less than 60% of the total dose being administered.²³ Activated charcoal also is available as a powder for reconstitution into an oral suspension just before use; this product should be stirred thoroughly or shaken vigorously after water is added. Flavoring agents have been used to try to increase the palatability of activated charcoal. Activated charcoal capsules or tablets marketed as a dietary supplement for GI symptoms or other ailments should not be used to manage poisonings, because the surface area of charcoal in these products is too small to effectively adsorb toxins.

Table 21-2 Activated Charcoal Dosing Information

Age	Dose
0–12 months ^a	10–25 g
1–12 years	25–50 g
> 12 years	25–100 g

^a Used primarily in a health care setting in this age group.

Source: Reference 22.

The most common adverse effects of activated charcoal are vomiting and black stools. Vomiting occurs in 12%–20% of patients receiving activated charcoal.²² One fifth of children younger than 18 years who were given activated charcoal for poisoning vomited at a median of 10 minutes after initiation of charcoal administration. More serious complications, such as pulmonary aspiration and GI obstruction, are associated more often with administration of multiple doses of activated charcoal.

Use of activated charcoal is contraindicated in patients in whom the GI tract is not anatomically (e.g., secondary to caustic injury) or functionally (e.g., ileus)

intact. After bariatric surgery, patients may not tolerate charcoal or may need smaller, more frequent doses. Activated charcoal also is contraindicated in patients at high risk for aspiration without airway protection ([Table 21-1](#)). Activated charcoal should not be administered after ingestion of substances that it does not adsorb unless the presence of other ingestants that are adsorbed by charcoal is suspected.

Pharmacotherapeutic Considerations for Activated Charcoal

Studies have demonstrated that the effectiveness of GI decontamination decreases significantly with increasing time interval since ingestion. For most overdoses, GI decontamination with activated charcoal should be performed early, usually within 1 hour of the ingestion.²⁴⁻²⁶

There is no convincing evidence that activated charcoal improves patient outcomes, and its utility in adults who intentionally overdose has been questioned, particularly in patients with mild to moderate poisoning.^{26,27} In some subgroups of patients with severe poisoning, activated charcoal may be beneficial; however, self-treatment has no place in the management of such poisonings.²⁶ A position statement by the American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists concluded that activated charcoal may be considered for a potentially toxic amount of a poison ingested up to 1 hour before treatment. Insufficient data are available to support or exclude use of charcoal when poison ingestion occurred more than 1 hour previously.²² A majority of studies on which the position statement was based were conducted in a controlled research or hospital environment. A Cochrane Systematic Review on first aid interventions by laypersons for acute poisoning identified uncertainty about the effect of single-dose activated charcoal compared with no intervention on the incidence of adverse effects in general, incidence and severity of poisoning, and rate of intensive care unit (ICU) admissions, as well as drug absorption²⁸

Although activated charcoal is sold as a nonprescription drug, it is not available in most homes, nor is it routinely recommended for home use by poison control centers. The American Academy of Pediatrics does not recommend maintaining a supply of activated charcoal in the home as part of its anticipatory guidance for poisoning. Sometimes activated charcoal is given in

the home setting to provide early prehospital GI decontamination in patients who subsequently are transported to a hospital emergency department. Health care providers should consult their local poison control center to determine whether to promote routine availability of activated charcoal in the home.

To date, experience with home administration of activated charcoal has shown it to be relatively safe. GI effects have been reported, with vomiting as the main adverse effect. Before any recommendation for use of activated charcoal, the health care provider should consult a poison control center.

Assessment of Poisoning: A Case-Based Approach

After obtaining the history of the exposure to a poison and performing an initial assessment of the patient's condition, the health care provider must decide whether to refer the patient directly to an emergency treatment facility, to manage the case in the home environment, or not to recommend any specific treatment. Clearly, patients with serious clinical effects including altered mental status (e.g., stupor, coma, seizures, agitation, hallucinations), respiratory distress, or changes in cardiovascular status (e.g., syncope, hypotension) are not candidates for self-care and should be transported immediately to the emergency treatment facility. Alternatively, recognizing nontoxic or minimally toxic exposures that can be managed outside a health care facility is an essential component of self-treatment for poisoning. Involving the poison control center in this assessment and treatment decision is important, because staff at such centers have considerable experience managing poisoned patients and specialized resources that are not usually available to providers. The nationwide toll-free poison control center number, 800-222-1222, connects callers to the center that serves their area ([Figure 21-1](#)).

Self-treatment at home is primarily intended for unintentional poison exposures in children younger than 6 years in whom no or, at most, minimal toxicity is expected. In addition, some unintentional therapeutic dosing errors, or inhalation or skin or eye exposures in any age group, with possible minimal toxicity, often are amenable to self-treatment.

For any patient inquiries about purchasing activated charcoal, the pharmacist must determine whether intended use of such preparations is for an acute situation, in which case the poison control center should be contacted to assess the appropriateness of self-treatment. The poison control center will need information about the patient (age, weight, medical history, any ongoing clinical effects), the toxin (name of the offending drug or other substance, dose, route of exposure, time since exposure), and what treatment, if any, has already been administered.

Cases 21–1 and 21–2 provide examples of assessment of two different patients who have experienced a potentially toxic exposure.

Case 21–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	A mother calls the pharmacist and asks what to do for her 2-year-old son, who just ingested a naproxen 220 mg tablet that was placed on the counter to give a teenaged sibling. Only one 220 mg tablet was available. The ingestion happened 5 minutes ago. The son is currently active and playful and does not appear to be in any distress.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	The mother stuck her finger down the back of her son's throat to induce vomiting, but no pill or pill fragments were seen in the vomitus.
c. Description of the patient's efforts to relieve the symptoms	n/a
d. Patient's identity	Jackson Smart
e. Patient's age, gender, height,	2 years, male, 34 in., 26 lb (12 kg)

and weight	
f. Patient's occupation	n/a
g. Patient's dietary habits	Normal
h. Patient's sleep habits	Sleeps approximately 12 hours a night and usually has a 1-hour nap at midday.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Healthy; takes no medications.
j. Allergies	No known allergies
k. History of other adverse reactions to medications	None
l. Description of other medications or products in the vicinity	No other medications or products present were identified by the patient's mother.
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Acute unintentional ingestion of no more than 220 mg (18.3 mg/kg) of naproxen
3. Identify exclusions for self-treatment (Figure 21-2).	The mother is well known to the pharmacist, and child abuse is not suspected. Therefore, there are no exclusions for self-treatment.
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer the patient to a hospital emergency department for possible GI decontamination and further evaluation. (2) Contact the poison control center for recommendations. (3) Have the patient's mother administer an over-the-counter treatment to decrease drug absorption at home.

	(4) Have the patient's mother administer oral fluids to dilute the naproxen. (5) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient or caregiver preferences.	Contact the poison control center for recommendations.
6. Describe the recommended therapeutic approach to the patient or caregiver.	The mother should be directed to call the poison control center at 800-222-1222.
	"The poison control center specialist can quickly assess the situation and determine whether it is safe to manage this situation at home or whether a trip to the emergency department is necessary. The maximum amount of naproxen that was available is 220 mg, or 18.3 mg/kg. This is likely below the threshold for referral for most poison control centers."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Naproxen may be irritating to the stomach. However, it is best to discuss this with the poisoning experts, who can quickly assess whether or not Jackson is likely to experience any adverse effects and tell you what to watch for."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	Criterion does not apply in this case.
Solicit follow-up questions from the patient or caregiver.	"I have activated charcoal at home. Should I give it to Jackson to be on the safe side?"
Answer the patient's or	"No—do not give activated charcoal unless directed by the

caregiver's questions.	poison control center. In many situations it is not necessary or may introduce other risks such as injury from vomiting."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	n/a

Key: GI = Gastrointestinal; n/a = not applicable.

Case 21-2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient is a 26-year-old man who brings 8 bottles of loperamide to the pharmacy register for purchase. When the pharmacist asks why he is buying so many bottles, the patient admits to using 300–400 mg of loperamide recreationally daily, to "get high." He took approximately 80 mg of loperamide 1 hour before coming to the pharmacy. He appears pale and shaky. He then complains of generalized weakness, dizziness, and nausea and asks about treatment options.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	On those days when he uses larger doses of loperamide (up to 600 mg), he sometimes feels worse. He mentions that occasionally he feels that he has a rapid heartbeat.

c. Description of the patient's efforts to relieve the symptoms	He states that he sometimes feels better lying down.
d. Patient's identity	Eric Jones
e. Patient's age, gender, height, and weight	26 years old, male, 6 ft 1 in., 201 lb (91.4 kg)
f. Patient's occupation	Construction worker
g. Patient's dietary habits	Normal
h. Patient's sleep habits	Sleeps approximately 6 hours a night.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Mr. Jones injured his back on the job several months ago; he initially was treated with acetaminophen/hydrocodone, then with ibuprofen. He no longer has a prescription for acetaminophen/hydrocodone. He uses an albuterol inhaler occasionally for exacerbations of asthma.
j. Allergies	No known allergies
k. History of other adverse reactions to medications	None
l. Description of other medications or products in the vicinity	No other medications or products are identified by the patient.
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Chronic misuse/abuse of dangerously high doses of loperamide for its psychoactive effects and possibly to alleviate opioid withdrawal subsequent to use of prescription opioids for back injury. It is possible that Mr. Jones's weakness, dizziness, and palpitations are due to dysrhythmias associated with high doses of loperamide.
3. Identify exclusions for self-treatment (Figure 21-2).	This is an abuse situation with possibility of life-threatening dysrhythmias, which is an exclusion for self-treatment.
4. Formulate a comprehensive list of therapeutic alternatives	Options include (1) Refer the patient to an emergency department for

for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	possible GI decontamination, ECG, and evaluation. (2) Contact the poison control center for recommendations. (3) Take the patient's blood pressure and pulse in the pharmacy and recommend a nonprescription product such as meclizine for nausea and dizziness. Recommend that he taper his use of loperamide. (4) Recommend oral fluids and refer the patient to a substance abuse counselor immediately. (5) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Refer Mr. Jones to a hospital emergency department for evaluation and treatment.
6. Describe the recommended therapeutic approach to the patient or caregiver.	The pharmacist should inform Mr. Jones that he needs to be seen in the closest hospital emergency department immediately for evaluation and treatment.
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"You are using a toxic dose of loperamide and may be experiencing serious cardiac effects. It is not safe to treat you with an over-the-counter product. You must go immediately to the closest hospital emergency department."
Implement	
8. When recommending self-care with nonprescription medications and/or	Criterion does not apply in this case.

nondrug therapy, convey accurate information to the patient or caregiver.	
Solicit follow-up questions from the patient or caregiver.	"I would like to go home and lie down. If I don't feel better in a few hours, I'll go the emergency department. Is that okay?"
Answer the patient's or caregiver's questions.	"No—immediate evaluation is critical. I will call 911 for you now."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	n/a

Key: ECG = Electrocardiography; GI = gastrointestinal; n/a = not applicable.

Patient Counseling for Poisoning

With inhalation exposures, after patients are removed from toxic fumes, they should be advised about when to seek medical attention (e.g., for difficulty breathing or worsening or persistent symptoms). In the home or other nonindustrial setting, fumes often are soluble, irritant gases (e.g., chlorine), so clinical effects are evident immediately and usually resolve soon after exposure stops. Patients also should be counseled on the need for thorough ventilation of the room to disperse the vapor. If the exposure resulted from mixing products such as bleach and ammonia, counseling should include a warning never to use such household products in combination. If carbon monoxide exposure is suspected, the patient should be instructed to have the source turned off or removed (e.g., malfunctioning furnace, stove, vehicle). The poison control center should be contacted to assess the severity and expected duration of clinical effects in symptomatic patients and the possibility of delayed onset in asymptomatic patients. Home carbon monoxide detectors are important home safety devices, and homeowners should be encouraged to install them to prevent or minimize carbon monoxide exposures.

With eye exposures, the patient should be counseled on how to irrigate the eye at home under the faucet. Contact lenses should be removed before irrigation. Instructions should include running the water at room temperature and at a low pressure. Irrigating the eyes in the shower or using a clean cup to pour water into the eyes may be an easier alternative in children. Placing a damp washcloth on the eye or irrigating with small-volume nonprescription eyewashes is ineffective. Finally, eye drops, including topical vasoconstrictors, should *not* be used after irrigation.

With skin exposures, the patient should be counseled to remove clothing in contact with involved skin, if necessary, and to wash affected areas thoroughly. With both eye and skin exposures, the importance of immediate irrigation and washing of the affected area, as appropriate, should be emphasized.

If the regional poison control center recommends activated charcoal for home use, pharmacies in that area should stock the appropriate product, and pharmacists should educate parents that activated charcoal should never be used without first consulting a poison control center staff member. Patients who purchase activated charcoal for immediate use on the recommendation of a poison control center should receive adequate counseling about this treatment to ensure appropriate use of the product, including instructions on preparation (depending on the formulation). The pharmacist also should explain potential adverse effects, as well as signs and symptoms that indicate the need to seek medical attention.

Counseling older adults on self-managing their medications can prevent poisonings and adverse drug reactions. Polypharmacy may place older adults at risk for errors relating to dose, dosage regimen, and possibly administration techniques. Educating these patients about the potential for interactions, including drug–drug, drug–food, and drug–alcohol, is important. They should be reminded to seek advice from an appropriate health care provider before mixing nonprescription or herbal products with prescription medications. Counseling older adults also should emphasize the importance of ongoing communication with their providers to ensure both efficacy and safety of their medication regimen.

Patients who are taking multiple prescriptions and using a regular “pill minder” should be advised to purchase a locking version if they are around young children. When loading the device, they should place a sheet of paper or cardboard underneath it to catch stray tablets or capsules that might

otherwise fall on the floor. Pharmacists also can prevent therapeutic 10-fold error types of poisonings by always dispensing 1 mL oral syringes for prescription medications that are dosed in infants at less than 1 mL, such as metoclopramide. The box “Patient Education for Toxic Exposures” lists specific information to provide in counseling parents, caregivers, or patients.

Counseling should include providing the nationwide toll-free number for the area-specific poison control center (Figure 21–1) and promoting poisoning prevention practices, including purchase of nonprescription drugs and household products with child-resistant packaging. However, caregivers should be reminded that child-*resistant* is not child-*proof*, even products with CRCs should be stored well out of reach and view of small children and preferably in a locked cabinet. The Up and Away campaign (www.upandaway.org) is a child safety initiative developed by PROTECT (Preventing Overdoses and Treatment Errors in Children Taskforce), a public–private collaboration, in partnership with the Centers for Disease Control and Prevention.

Evaluation of Patient Outcomes for Poisoning

Patients who have inhaled potentially toxic fumes or spilled or splashed a substance on their skin or in their eyes should be reassessed for symptoms after removal to fresh air or irrigation of the affected area. If clinical effects are minimal and resolve within a relatively short period (e.g., <30 minutes), the patient may be observed at home. If symptoms persist or worsen, the patient should be referred to a health care provider or an emergency department, depending on the severity of symptoms and apparent immediacy of need for medical evaluation. The poison control center can facilitate the referral to the appropriate health care facility and provide treatment recommendations to the health care provider.

Patients who receive activated charcoal, or their caregivers, should be contacted afterward at least once to determine whether any symptoms related to the exposure have developed. The timing of the call depends on what substance was ingested, how rapidly it is absorbed, and when emergence of symptoms would be anticipated. If clinical effects develop and are minor, the patient may be observed at home. If more significant effects develop, the patient should be referred to an emergency department for

treatment. If the poison control center recommended self-treatment with activated charcoal, the center staff should remain involved in subsequent decisions regarding the appropriateness of continued at-home treatment for the patient.

Patient Education for Toxic Exposures

The objectives of self-treatment are (1) to minimize exposure and reduce development of toxicity by removing the patient to fresh air, irrigating the skin or eyes, or preventing absorption of potentially toxic agents in the gastrointestinal (GI) tract and (2) to manage patients with minimally toxic ingestions at home under the supervision of a poison control center. With most toxic exposures, carefully following the self-care measures listed here will help ensure optimal therapeutic outcomes.

Treatment

- For eye exposures, immediately irrigate with water for 10–15 minutes.
- For skin exposures, immediately wash with soap and water.
- For inhalation exposures, immediately remove the patient to fresh air.

When to Seek Medical Attention

- Referral to a hospital emergency department by contacting 911 directly is appropriate if the patient
 - Is lethargic or comatose or is having convulsions or hallucinations
 - Has decreased respirations or is having difficulty breathing
 - Has abnormal blood pressure or pulse
 - Has taken medications that may produce a rapid decline in consciousness or convulsions

Key Points for Poisoning

- Poison exposures are a common cause of pediatric and adult injury.
- Persons who purposely misuse, abuse, or use medications as a means of self-harm are not candidates for self-care and should be referred for medical care on an urgent basis.
- All patients who exhibit potentially life-threatening clinical effects (e.g., seizures, coma) should be referred to a hospital emergency department through the emergency 911 system.
- Medication errors are a common cause of drug-related toxicity, especially in persons at the extremes of age (infants and older adults).
- Minimizing the duration or limiting the extent of the exposure is the rationale for most self-treatment practices.
- No evidence has emerged showing that self-treatment for poisoning with activated charcoal improves patient outcomes. This treatment should be used only on recommendation of a poison control center.
- Self-treatment should be considered only for unintentional poison exposures that are likely to cause no or minimal toxicity—that is, no serious or life-threatening symptoms ([Figure 21-2](#)).
- The health care provider should consult with the poison control center for guidance on patient assessment and on decisions for the appropriateness of self-treatment.
- Direct referral to a poison control center should be considered for complicated cases, including those in which the patient history is unclear or specific product or toxin information is lacking, and to ensure patient follow-up.

Chapter 22: Ostomy Care and Supplies

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An *ostomy* is an opening or outlet through the abdominal wall created surgically for the purpose of eliminating waste. The ostomy usually is made by bringing a portion of the bladder, colon, small intestine, or ureter out through the abdominal wall. This abdominal opening is called the *stoma* (the Greek word for “mouth”).

The establishment of an ostomy, temporary or permanent, to replace normal elimination anatomy may be a dramatic, life-changing event. The health care provider is a crucial resource for the reassurance, support, and education needed by the patient and family. Understanding improvements in surgical procedures, ostomy supplies, and outcomes can help allay the patient’s fear and anxiety. The goal in ostomy care is to enable resumption of the previous lifestyle as much as possible—to be a person, not a patient. In encounters with providers, the person with an ostomy will notice their reaction to the presence of the stoma. Any negative response—even unconscious signals such as a hurried interaction or avoidance of eye contact—may contribute to the patient’s difficulties with altered self-image related to the ostomy, so special care should be taken to convey acceptance and knowledgeability about various aspects of stoma management.

More than 725,000 to 1 million Americans are currently living with an ostomy.¹ Ostomy surgery is performed in people of all ages and for many conditions, both acquired and congenital. When medically advisable, the current trend is laparoscopic surgery, a type of minimally invasive surgery that uses smaller-scale instruments, placed through minor incisions, with the assistance of video camera technology. Patients report experiencing less pain, quicker recovery, and less scarring than with traditional ostomy surgery.

Indications for Ostomies

Ostomies may be permanent or temporary, and ostomy surgery is performed in all age groups, ranging from neonates to older adults. Reasons for needing an ostomy include congenital anomalies (e.g., imperforate anus, Hirschsprung

disease), inflammatory bowel disease (i.e., ulcerative colitis and Crohn's disease), familial polyposis, cancer, radiation damage, pressure injuries, trauma, and any other conditions necessitating diversion of the urinary or fecal stream.²⁻⁴ The type of ostomy depends on the underlying disorder or condition being treated.

The two most common disorders leading to *ileostomy* surgery are (1) ulcerative colitis, which affects the large intestine and rectum, and (2) Crohn's disease, which may involve any part of the gastrointestinal (GI) tract. Other conditions that may result in need for an ileostomy are traumatic injury, cancer, familial polyposis, and necrotizing enterocolitis.

The most common reasons for *colostomy* surgery are (1) cancer of the colon or rectum, (2) diverticulitis, and (3) traumatic injury. Other indications are obstruction of the colon or rectum, genetic malformation, radiation colitis, and fecal incontinence. In some cases, a temporary colostomy may be placed to protect areas of the colon that have been surgically repaired. Healing of diseased or damaged bowel may take several weeks, months, or years, but eventually the colon and the rectum are reconnected and bowel continuity is restored. [Figure 22-1](#) shows the location of various types of colostomies.

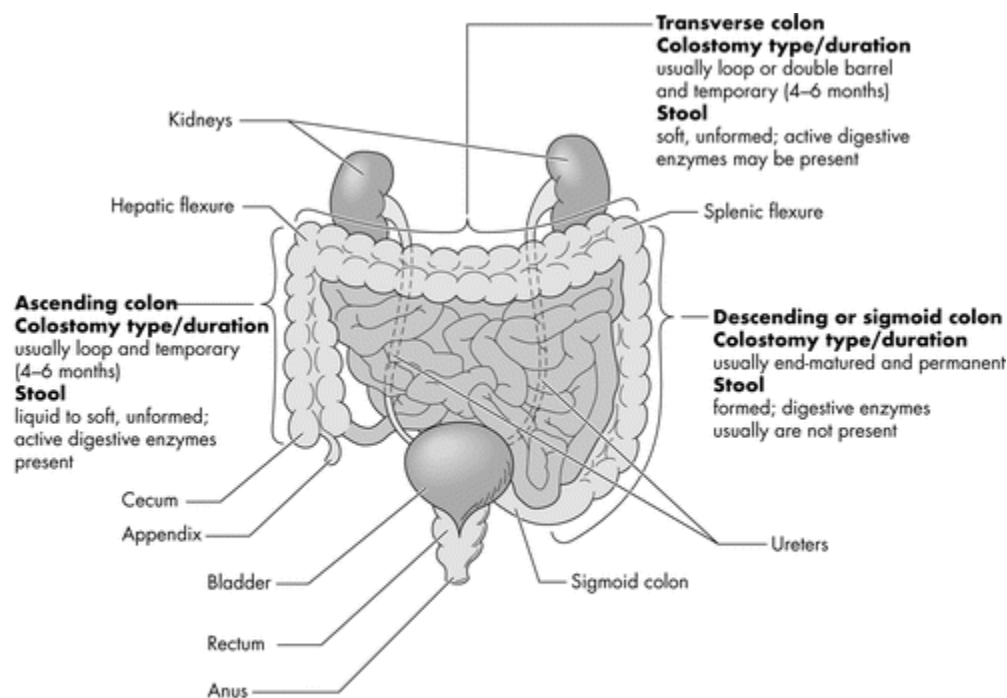


Figure 22–1 Anatomic drawing of the lower digestive and urinary tracts depicting location and permanence of colostomies. (Source: Adapted with permission from *Am J Nurs.* 1977;77:443.)

Urinary diversions, or *urostomies*, are created to correct bladder dysfunction or to restore functionality after bladder loss, which can be secondary to cancer, neurogenic bladder, genetic malformation, or interstitial cystitis.

Types of Ostomies

The three basic types of ostomies are (1) ileostomy, (2) colostomy (the most common type), and (3) urostomy (see [Color Plates](#), photographs 6A–I). Each type has several variations, depending on the location of the stoma, the reason for the surgical procedure, or whether the procedure will maintain urinary or fecal continence.

Ileostomy

An ileostomy is surgically created by bringing a portion of the ileum through the abdominal wall (see [Color Plates](#), photograph 6A). Initially, the discharge is liquid, but as the ileum adapts, it assumes some of the absorptive functions of the colon and the discharge may become semisoft. The discharge is continuous and contains digestive enzymes that may irritate the peristomal skin.

Several types of continent ileostomies have been devised (see [Color Plates](#), photograph 6B). Typically, an internal pouch is created from the ileum, and an intussusception (a slipping of a length of intestine within an adjacent portion) of the bowel is used to create a “nipple” that renders the patient continent for stool and flatus. The pouch is periodically emptied by inserting a catheter through the nipple, which is attached to the skin usually in the right lower abdominal quadrant, into the pouch. At first, the pouch holds approximately 75 mL, but it stretches with use, so that at 6 months postoperatively, it may hold 600–800 mL and can be drained 3–5 times daily. Patients do not need to wear an external pouching system, but they often use a gauze pad or stoma cap over the opening.

The restorative proctocolectomy (S pouch or J pouch, named for the resulting

anatomic configuration) with ileoanal reservoir spares the rectum in patients with ulcerative colitis or familial polyposis. The colon is removed and the diseased mucosa is stripped from the rectum, and an internal pouch is created from the ileum. The distal end of the small intestine is stapled or hand sewn to the remaining rectal tissue. The sphincter is preserved, and ostomy pouching systems are unnecessary. However, a patient undergoing this procedure may have a temporary stoma (for approximately 3–6 months) placed to protect the healing pouch. After ileoanal reservoir surgery, bowel movements will be more frequent, and the patient may experience perianal skin irritation.

Colostomy

A colostomy is created by bringing a portion of the colon through the abdominal wall. The discharge may be semisoft, paste-like, or formed, depending on the portion of bowel used ([Figure 22-1](#)).

Ascending colostomies are uncommon. The ascending colon is retained, but the rest of the large bowel is removed or bypassed (see [Color Plates](#), photograph 6C). The stoma usually is placed on the right side of the abdomen. The discharge is similar to that with an ileostomy—semisoft—and a pouch must be worn at all times.

The *transverse* colon is the site of most temporary colostomies ([Figure 22-1](#)). A loop of the transverse colon is lifted through the abdominal incision, and a rod or bridge (which is removed within 1–2 weeks) is placed under the loop to give it support while the stoma heals. The discharge usually is semiliquid or very soft and contains digestive enzymes.

Loop colostomies have one large opening but two tracts (see [Color Plates](#), photograph 6D). The proximal tract discharges fecal material, and the distal tract secretes small amounts of mucus. A pouching system must be worn at all times. A person with a loop colostomy also may pass a minimal amount of stool or mucus through the rectum as a normal occurrence.

For a *double-barrel transverse* colostomy, the bowel is completely divided by bringing both the proximal end and the distal end through the abdominal wall and then suturing them to the skin (see [Color Plates](#), photograph 6E). The distal stoma also may be called the mucous fistula.

Descending and *sigmoid* colostomies are fairly common; generally the stoma

is placed on the left side of the abdomen (see [Color Plates](#), photograph 6F). The fecal discharge has a paste-like consistency and at times may consist of formed stool. This type of colostomy may be regulated by irrigation; therefore, a pouching system may or may not be needed. However, many patients prefer a pouch to irrigation. Not everyone with a descending or sigmoid colostomy is a good candidate for irrigation or prefers irrigation. Factors to consider in making the decision to irrigate include the presence or absence of stomal complications and the patient's normal stooling pattern, psychomotor ability, and willingness to commit the time required to properly irrigate the ostomy.

Urinary Diversions

Urinary diversion surgery creates an alternative route for discharge of urine through an opening in the abdominal wall. Urinary stomas should function immediately after surgery. The broad term for a urinary diversion is *urostomy*.

The *ileal conduit* is the most common type of urinary diversion (see [Color Plates](#), photograph 6G). After the bladder is removed, ileal or colon conduits are created by implanting the ureters into an isolated loop of bowel; one end of the bowel loop is sutured, and the distal end is brought to the surface of the abdomen. The stoma looks similar to an ileostomy or colostomy stoma. A pouching system must be worn continuously. Mucous shreds will be present in the urine when the small intestine or the large intestine is used to create the diversion (see [Color Plates](#), photograph 6H). Because the ileum is used to create an ileal conduit, some people incorrectly refer to the ileal conduit as an ileostomy. Clarification of the type of effluent (stool or urine) will help in selecting the correct type of pouch.

In a *ureterostomy*, one or both ureters are detached from the bladder and brought to the outside of the abdominal wall, where a stoma is created. This procedure is used less frequently because the ureters tend to narrow unless they have been dilated permanently because of previous disease (see [Color Plates](#), photograph 6I).

A *cystostomy* is performed when blockage or narrowing of the urethra occurs. Urine is diverted from the bladder to the abdominal wall. A pouch must be worn continuously. An infant with a cystostomy may wear diapers instead of a pouch.

The *continent urinary diversion* is available for selected patients, but its use requires that certain criteria be met. An Indiana pouch is a type of continent urostomy in which a reservoir is created from part of the cecum and ileum, with a portion of the ileum brought through the abdominal wall to create a stoma. The ureters are attached to the cecum pouch. The remaining ileum is reattached to the colon for normal digestive flow. The ileocecal valve is left intact and becomes part of the continence mechanism, preventing urine from exiting the pouch. The internal pouch is emptied by inserting a catheter into the stoma to drain the urine. Patients usually follow a strict schedule for catheterizing the stoma often enough to avoid leakage. The new pouch may hold up to 600 mL of urine. An external pouching system is not necessary. Most patients wear a gauze pad or stoma cap.

The *orthotopic neobladder* is a rebuilt bladder. The small intestine is used to create a pouch, and the pouch is then attached to the native urethra. This procedure allows patients to void using the urethra, but voiding relies on use of the abdominal muscles to empty the neobladder.

Algorithm: Selection of Ostomy Pouching System

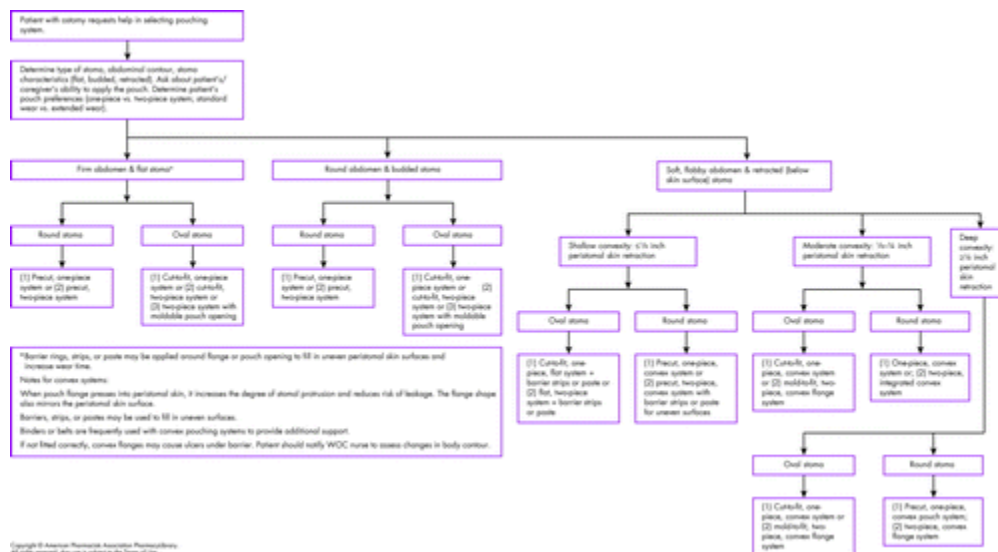


Figure 22–2 Selection of ostomy pouching system. Key: WOC = Wound, ostomy, and continence.

Management of Ostomies

Management Goals

The ideal pouching system should maintain a seal for a predictable amount of time (average wear time is 3–4 days) and protect the peristomal skin. All pouches are odor proof and are available with a variety of features such as opaque versus clear, drainable versus closed-end, and so on. The pouching system collects the stoma output until it is convenient for the person with the ostomy to empty or remove the pouch. The goal is to have no leakage (with a secure seal) and to maintain the peristomal skin. If the peristomal skin becomes irritated, achieving a good seal on the pouching system is very difficult, potentially resulting in leakage and pain around the stoma, with consequent distress to the patient.

The ostomy industry is highly specialized and rapidly changing as researchers and manufacturers try to improve designs, resulting in a wide range of choices. Pouch selection is based upon the type of stoma, its location on the abdomen, the peristomal skin contours, and the patient's self-management abilities.

General Management Approach

Patients and/or their caregivers should be taught self-care skills to manage the ostomy, including (1) sizing the stoma, (2) cutting a skin barrier to fit the stoma (or selecting a precut pouch or barrier), (3) cleaning the peristomal skin, (4) choosing and using accessory products, (5) applying the pouch, (6) removing the pouch, and (7) emptying the pouch.

Patients are most likely to achieve optimal outcomes if the pouching system is properly fitted ([Figure 22–2](#)) and if the stoma is cared for appropriately. In interactions with persons with an ostomy, the health care provider should always be aware of the sensitive nature of the topic and ensure that privacy is respected during all encounters. Lack of a comfortable environment in which to discuss problems, concerns, and alternatives may induce patients to avoid such discussions, with less-than-optimal outcomes. Follow-up assessment and care may be accomplished through a telephone call or scheduled appointment or during the patient's routine pharmacy visits to purchase supplies or medications.

As noted, the pouching system should remain in place for a predictable period of time, usually at least 3 days. Frequent changes of the pouching system may signal a potential problem. In many cases, patients may be referred to an appropriate primary care provider or a wound, ostomy, and continence (WOC) nurse specialist for follow-up evaluation and treatment of problems identified by the initial health care provider. Problems such as inability to maintain a pouch seal for a predictable amount of time or development of a peristomal hernia, stenosis, prolapse, retraction, or peristomal skin injury warrant referral.

The presence of an ostomy and its location in the GI or urinary system should always be noted in the patient's profile, to minimize medication-related risks. It is helpful to maintain a record of current and past ostomy products with order numbers that the patient has used and any problems that the patient has experienced. This information can be helpful in making future recommendations or to assist in problem solving.

Types of Ostomy Pouching Systems

A large variety of pouching systems are available, and the choice of a pouching system will depend upon the size and shape of the stoma, the location of the stoma opening, the type of effluent from the stoma (urine, pasty or liquid stool), the contours of the peristomal skin, and patient preferences and abilities.

The components of a pouching system include a skin barrier, which provides the skin protection and adhesive seal, and the pouch. and are available in a one- or two-piece system (Figure 22–3). With a one-piece system, the skin barrier and the pouch are nondetachable from each other; with a two-piece system, the skin barrier is separate from the pouch, and the pouch is attached to the skin barrier by an adhesive or flange coupling system.

Figure 22–3 Sample ostomy appliances: A: Coloplast SenSura Mio urostomy pouch; B: Coloplast SenSura Mio drainable pouch; C: Coloplast SenSura Mio closed-end pouch; D–F: Hollister New Image two-piece pouching system with Lock’n Roll closure, flange and pouch views, respectively. (Source: A–C reprinted with permission from Coloplast, Minneapolis, MN; D–F reprinted with permission from Hollister Incorporated, Libertyville, IL.)

Both one- and two-piece pouching systems are available in drainable, closed-end, and urostomy styles. Drainable pouches allow the user to open the end of the pouch to empty the contents into the toilet. A closed-end system requires the wearer to remove and discard the pouch when about 3/4 full. Closed-end systems can be used by patients who have one or two formed bowel movements within 24 hours, or who routinely irrigate the ostomy to remove output. Most insurers will reimburse the user for two closed-end pouches per day. Urostomy systems allow easy emptying throughout the day through a valve at the bottom of the pouch. At night, most urostomy patients connect their pouch to dependent drainage, to prevent overfilling of the pouch.

Fit and Application

The fit of the pouching system is critical to ensure peristomal skin protection and a secure seal. The stoma is measured at the skin stoma junction to ensure that all of the skin is protected. If the stoma is round, the opening in the pouching system also will need to be round; if the stoma shape is other than round, the opening should be cut (or in some cases molded) to the typically oval shape.

The shape of the skin barrier also is a decision point for choosing a pouching system. Skin barriers are available in flat or convex. When the patient is fitted for a skin barrier, the area around the stoma is assessed in sitting, standing, and reclining positions; in each position, the skin barrier should be a mirror image of the peristomal skin contours. If the area around the stoma is flat in all positions, the skin barrier chosen will be flat; if the area around the stoma is concave, the skin barrier of choice will be convex. Another consideration in choosing the shape of the skin barrier is the protrusion of the stoma: If the stoma does not have adequate protrusion above the skin, a convex barrier may help achieve a secure seal, as the convexity can help apply light pressure to allow the stoma to protrude into the pouching system.

Pouch options include clear versus opaque, length (in a range of 7–16 inches), various types of closures, presence or absence of a gas filter, and drainable versus nondrainable (closed-end). The choice of pouch depends upon patient preference (with recognition that the skin barrier is the portion of the pouching system that provides security and peristomal skin protection) and may be dictated by the volume of stoma output (the shorter the pouch length, the more often it may need to be emptied), requirement for visibility of the

stoma effluent to determine when or whether to empty/change the pouch, and level of daily activity of the person with the ostomy.

Directly after surgery, a cut-to-fit pouch maybe used until the stoma heals, because the stoma will shrink as the postoperative edema lessens.

Immediately after surgery, the patient is learning self-care and moving toward adjustment. On becoming more comfortable with how to manage the stoma, the person will participate in making choices about the best pouching system. A WOC nurse is an excellent source of assistance in custom-fitting pouching systems.

Wear Time

Wear time for the pouching system is determined by the integrity of the skin barrier. The skin barrier is constructed from a material called a *hydrocolloid*. The hydrocolloid softens in the presence of moisture. As softening occurs, less functional adhesive is available to secure the seal. A person with a high liquid output or very moist skin (as from heavy perspiration) may find that the skin barrier must be changed in 3–4 days. A person with solid to semisolid stool may be able to wear the skin barrier longer than 4 days. Patients are taught to inspect the back of the skin barrier upon removal. On observation, if the opening in the skin barrier is significantly larger than it was on application, this may be a sign that erosion of the seal has occurred, which could allow the stoma effluent to make contact with the skin, with consequent leakage and skin irritation. Although activities such as swimming or playing tennis may decrease the wear time of the pouch, this decreased time should not discourage participation in physical activities. More recently developed pouch adhesives can effectively keep the system in place during these activities.

Product Selection Guidelines

The selection of products should be customized to achieve best care for the patient's stoma and peristomal area. For instance, some systems require manipulation that a patient with arthritis may not be able to perform. Patients may have other special needs, such as those related to visual impairment or, conversely, to expectations for participation in high levels of physical activity in water sports. [Table 22–1](#) lists ostomy manufacturers, with addresses for websites that detail available products and product information.

Table 22-1 Sources of Ostomy Support, Products, and Information

Organization/Manufacturer	Telephone Number	Website
American Cancer Society	800-ACS-2345	www.cancer.org
Colo-majic Liners	866-611-6028	www.colomajic.com
Coloplast	800-533-0464	www.coloplast.com
ConvaTec	800-422-8811	www.convatec.com
Crohn's and Colitis Foundation	800-343-3637	www.crohnscolitisfoundation.org
Cymed Ostomy Company	800-582-0707	www.cymed-ostomy.com
C&S Ostomy Pouch Covers	877-754-9913	www.cspouchcovers.com
Hollister, Inc.	800-323-4060	www.hollister.com
Hy-Tape Corporation	800-248-0101	www.hytape.com
International Ostomy Association	n/a	www.ostomyinternational.org
Kem-Osto EZ-Vent	888-562-8802	www.kemOnline.com
Marlen Manufacturing	276-292-9196	www.marlenmfg.com
Nu-Hope Laboratories, Inc.	800-899-5017	www.nu-hope.com
Options Ostomy Support/ Barrier, Inc.	800-736-6555	www.options-ostomy.com
Ostomysecrets	877-613-6246	www.ostomysecrets.com
Schena Ostomy Technologies	239-263-9957	www.ostomyezclean.com
Safe n' Simple	248-214-4877	www.SnS-medical.com
Stealth Belt	800-237-4491	www.stealthbelt.com
Stoma Guard	800-814-4195	www.sto-med.com
The Parthenon Company, Inc.	800-453-8898	www.parthenonInc.com
Torbot Group, Inc.	800-545-4254	www.torbot.com
United Ostomy Associations	800-826-0826	www.ostomy.org

Organization/Manufacturer	Telephone Number	Website
of America, Inc.		
United Ostomy Association of Canada, Inc.	416-595-5452; 888-969-9698 (Canadian residents only)	www.ostomycanada.ca
Wound, Ostomy and Continence Nurses Society (WOCN)	888-224-WOCN	www.wocn.org

Ostomy Accessories

Belts

Some pouching systems have belt tabs, which allow attachment of a belt for additional support. Indications for the use of a belt may be a convex flange, as the belt can help to press the adhesive to the skin; high activity level (e.g., running), for which the belt will provide better adherence; and personal preference. Some patients may find that wearing a belt for just a few hours after pouch application helps to enhance the seal, decreasing the risk of subsequent leakage.

Skin Barrier Rings, Powder, Paste, Barrier Strips

Skin barrier rings, powder, paste, and barrier strips are accessories that can be used to enhance the pouching system seal and manage peristomal skin complications ([Table 22-2](#)). Skin barrier rings can be used to provide a seal around the stoma in patients with a fecal stoma and increase wear time. Skin barrier powder is a hydrocolloid that can dry moist peristomal skin, support healing, and enhance the seal in problematic situations involving denuded peristomal skin. Skin barrier powder is applied to the irritated skin and gently rubbed in, and the excess is brushed off. Leaving loose powder on the skin may interfere with the pouching system adhesive seal. A liquid skin barrier can be used to seal the powder. Skin barrier paste (again a hydrocolloid) can be used to fill a crease on the peristomal skin or to caulk the inner opening of the skin barrier on the pouching system, to secure the seal. Skin barrier strips can be placed on the outer seal, to secure the edges of the pouch.

Table 22-2 Ostomy Products With Selected Manufacturer Examples

Product	Example(s) of Manufacturer Products With Purpose/Use
Pouch deodorant	Hollister Adapt Lubricating Deodorant, Brava Lubricating Deodorant
	<i>Also facilitates emptying of pouch by providing lubrication in the pouch.</i>
	Hollister M9 Drops
	<i>Placed in pouch to neutralize odor.</i>
Liquid skin barrier	ConvaTec Sting Free Barrier Wipes, Smith and Nephew No Sting Barrier Wipes
	<i>Place on skin for protection or to seal skin barrier powder.</i>
Barrier rings	Coloplast Brava Protective Seals, Eakin Cohesive Seals, Hollister Adapt rings
	<i>Hydrocolloid rings stretched to fit around stoma for peristomal skin protection.</i>
Adhesive remover	Sensicare Sting Free Remover wipes, Adapt Universal Remover wipes
	<i>Removes residual adhesive from peristomal skin, facilitates pouch removal.</i>
Adhesive releaser	Sensicare Sting Free Adhesive Spray Releaser, Adapt Medical Adhesive Remover Spray
	<i>Used to release the pouch seal from the skin.</i>
Skin barrier paste	Stomahesive Paste, Brava Paste
	<i>Used to caulk edge of skin barrier also to fill in uneven areas.</i>
Skin barrier powder	Brava Ostomy Powder, Adapt Powder
	<i>Used to dry an injured skin surface.</i>
Barrier strips	Brava Elastic Barrier Strips, Adapt Barrier Extenders
	<i>Used to secure outer seal of pouching system.</i>
Osto-EZ-Vent	<i>Quickly and easily releases gas buildup in ostomy pouches.</i>
Hernia support	Brava Ostomy Support Belt, NuHope Hernia Support Belt, Security Hernia/

Product	Example(s) of Manufacturer Products With Purpose/Use
belts	Ostomy Support Belt
	<i>Provides support of peristomal hernia.</i>

Absorbent Gel Packets and Flakes

Absorbent gel packets and flakes placed in the pouch (e.g., Ileosorb, Par-Sorb) dissolve as the pouch fills, turning the liquid effluent into a gel. The use of these products can reduce noise caused by sloshing of stomal fluids, control odor, avert development of peristomal skin irritation, and prevent leakage, especially at night while the patient sleeps.

Cleansing and Special Skin Care Products

Cleansing of the stoma and surrounding skin is best done with plain water. If soap is used, it should be rinsed off thoroughly, and the skin should be dried before a new pouching system is applied. Use of moisturizers and products containing lanolin, petrolatum, or oils should be avoided because they prevent the pouching system from adhering to the skin.

Adhesive Removers and Releasers

The seal of the pouching system is created from hydrocolloids, and with erosion over time, hydrocolloid remnants can build up on the skin. Excessive adhesive on the skin also can prevent a good seal, and many people with an ostomy use nongreasy (usually silicone-based) adhesive removers to clean the peristomal skin. Adhesive releasers in spray or wipe form can be used to remove the pouch from the skin to prevent medical related adhesive skin damage.

Irrigation Kits

Irrigation is a method that can be used to maintain control of output in patients with colostomies. Irrigation is similar to performing an enema at the site of the stoma. The patient who has a left-sided (sigmoid or descending) stoma with no other bowel disease may be a candidate for irrigation. Because the goal of this management approach is no release of fecal material between

irrigation procedures, only patients with semisolid stools are candidates for irrigation. Using an irrigation kit (a bag with tubing that features a soft rubber cone), approximately 1000 mL of lukewarm tap water is instilled into the bowel through the cone inserted in the stoma. The bowel expands, causing peristalsis, with subsequent elimination of waste through the stoma.

Frequency of irrigation depends on the patient's normal bowel habits. The recommended approach is to irrigate at the same time every day and eventually to irrigate every other day. Establishing the irrigation regimen takes approximately 6 weeks. After achieving good control, the patient may wear a security pouch (in case stool or gas is discharged between irrigations). Elimination by irrigation is not necessary for health; it is merely one method of colostomy management. Patients who choose this procedure should be instructed in technique by a WOC nurse or their primary care provider.

Deodorizers

All pouching systems are odor proof; however, if the person with an ostomy notes odor even with the end of the pouch closed, the source of the odor may be leakage under the pouch seal. However, emptying a fecal pouch also will release odor from the effluent, and an important management concern for many people with an ostomy is to reduce this odor. Any of a variety of in-pouch deodorants, typically drops, can be placed into the pouch via the bottom. Most such products work by neutralizing the odor of the stool. When the pouch is emptied, the deodorant is also emptied, so more deodorant must be placed afterward. DevKo external tablets also may be placed into the pouch to decrease odor. Derifil internal deodorant tablets (active ingredient is 100 mg chlorophyllin copper complex sodium) may also be used. Of note, the purpose of such deodorizers is only to lessen odor during pouch emptying; no odor should be detectable when the pouch is on and adequately sealed.

Changes in Diet

Diet does not generally play an important role in ostomy management. Most patients can eat their usual diet, including all of the foods they ate before surgery if they chew everything well. A diet low in fiber is advisable for the first 6 weeks after surgery, however, to allow the intestine to heal and the swelling to resolve. The usual diet can be resumed after that time.

The effects of various foods on ostomy output are summarized in [Table 22–3](#). Patients with a urostomy may want to avoid foods that cause urine odor. Patients with colostomies, especially those who irrigate, should avoid foods that can cause loose stools. (This problem varies among individual patients.) Because they have no control over passage of gas, patients with a fecal ostomy may prefer to reduce their intake of gas-forming foods. Products such as alpha-D-galactosidase may be used to limit gas formation (see [Chapter 14](#)). Patients with ileostomies are more prone to intestinal obstruction from high-fiber foods eaten in large quantities or eaten exclusive of other foods ([Table 22–4](#)).^{5,6} Thoroughly chewing high-fiber foods and eating them in small amounts and with other types of food will help prevent food blockage. The patient should be instructed on how to manage a food blockage. [Table 22–5](#) lists signs and symptoms of blockage; [Table 22–6](#) summarizes its management.

Table 22–3 Effects of Foods on Stoma Output
Foods That Thicken Stool
Applesauce; bananas; bread; buttermilk; cheese; marshmallows; milk; pasta, boiled; peanut butter, creamy; potatoes; pretzels; rice; tapioca; toast; yogurt
Foods That Loosen Stool
Beer and other alcoholic beverages; chocolate; dried or string beans; fried foods; greasy foods; highly spiced foods; leafy green vegetables (lettuce, broccoli, spinach); prune or grape juice; raw fruits (except bananas); raw vegetables, fruit juices, milk
Foods That May Cause Stool Odor
Asparagus; beans; cabbage family vegetables (cabbage, Brussels sprouts, broccoli, cauliflower); cheese; eggs; fish; garlic; onions; some spices; turnips
Foods That May Cause Urine Odor
Asparagus; seafood; some spices
Foods That Combat Urine Odor
Buttermilk; cranberry juice; yogurt
Foods That Cause Gas
Beans (dried, string, or baked); apples; beer; cabbage family vegetables (cabbage, Brussels sprouts,

broccoli, cauliflower, kale); carbonated beverages; corn; cucumbers; dairy products; mushrooms; onions; peas; radishes; spinach; spicy foods

Foods That Color Stool

Beets; berries; chocolate; fats; fish; meat (large amounts of red meat); milk; red gelatin; vegetables; popsicles; licorice

Source: References 5 and 6.

Table 22-4 High-Fiber Foods^a

Apple skins	Grapes
Apricots	Mushrooms
Asparagus	Nuts
Beans and lentils	Oranges and orange rinds
Bologna	Pineapples
Bran	Popcorn
Celery	Potato peels
Chinese vegetables	Raisins
Coconut	Raw vegetables
Corn	Seeds
Dried figs	Shrimp
Grapefruit	Tomatoes

^a Limited or cautious consumption is indicated for persons with ileostomies.

Source: References 5 and 6.

Table 22-5 Signs and Symptoms of Intestinal Obstruction

Partial Obstruction	Complete Obstruction
Watery output with foul odor	Absence of output (urine and fecal)
Cramping abdominal pain	Severe cramping pain
Abdominal distention (possible)	Abdominal distention
Stomal swelling (possible)	Stomal swelling
Nausea and vomiting (possible)	Nausea and vomiting
	Decreased pulse rate

Source: References 5 and 6.

Table 22-6 Conservative Management of Food Blockage

1. Sit in warm tub bath to relax abdominal muscles.
2. Massage the peristomal area while in the knee-to-chest position to attempt dislodgement of fibrous mass.
3. If stoma is swollen, remove pouch and replace with a pouch that has a larger stoma opening.
4. If able to tolerate fluids (i.e., not vomiting) and passing stool, increase intake of fluid and electrolytes, but avoid solid foods. Drink 1 glass of liquid each time pouch is emptied. Juices such as grape juice exert a mild cathartic effect.
5. If vomiting, not passing stool, or both, do not take liquids or solid food orally and seek medical attention.
6. Notify a primary care provider or wound, ostomy, and continence nurse if any of the following is noted:
 - Stool output stops (indicating complete blockage).
 - Conservative measures (listed above) fail to resolve symptoms.
 - Signs of partial obstruction persist ([Table 22-5](#)).
 - Inability to tolerate fluids or replacement fluids and electrolytes becomes evident.
 - Signs and symptoms of fluid and electrolyte imbalance ([Table 22-7](#)) develop.

Source: Reference 5.

Complications of Ostomies

Persons with ostomies may experience both psychological and physical complications. The health care provider should be prepared to address these complications or to refer patients to their primary care provider or to a WOC nurse. These nurse specialists often are based in hospitals, clinics, or home health care agencies. The United Ostomy Associations of America is an organization that provides peer support for patients. Before surgery, patients should receive a thorough explanation that describes what procedure will be performed, what to expect during the postsurgical recovery period, and what pouching and supplies will be used and the proposed stoma site marking.

Psychological Complications

Some patients anticipating ostomy surgery fear that they will not be able to continue their former job, participate in sports, perform sexually, or have children. These patients need reassurance that an ostomy rarely impairs the ability to carry out such activities. Contacting the local United Ostomy Associations of America is of utmost importance in assisting with the rehabilitation of these patients; both providers and patients are encouraged to utilize the support of this organization. Patients also may wish to find a local WOC nurse. Before and after ostomy surgery, appropriate education and counseling on ostomy care will provide needed information and support. Literature is available from all of the major ostomy product manufacturers, the United Ostomy Associations of America, and the American College of Surgeons. If postoperatively the patient would benefit from contacting a mental health specialist, a referral to a clinician with experience in living with an ostomy is recommended.

Physiologic Complications

The major physiologic consequence of a GI ostomy is fluid and electrolyte imbalance. Such disturbances are most problematic in patients with a liquid or semisoft stoma discharge, such as with ileostomy and ascending or transverse colostomy. Patients with these types of ostomies must maintain adequate fluid intake to compensate for loss of the absorptive function of the colon and for absence of ileocecal valve function. Patients with ileostomies lose approximately 500–1000 mL of fluid daily through the stoma, whereas those with a normally functioning colon lose 100–200 mL daily.³ During common illnesses, patients with ileostomies, especially infants, are particularly vulnerable to fluid and electrolyte imbalance caused by vomiting and diarrhea.

Caregivers and patients should be educated about common signs and symptoms of a fluid and electrolyte imbalance ([Table 22–7](#)).^{5,6}

Table 22–7 Signs and Symptoms of Fluid and Electrolyte Imbalance	
Adults	Infants
Increased thirst	Depressed fontanel
Dry mouth and mucous membranes	Lethargy
Orthostatic hypotension	Sunken eyes
Decreased urine volume	Weak cry
Increased urine concentration (dark in color)	Decreased frequency of wet diapers
Sunken eyes	Increased urine concentration (dark in color)
Extreme weakness	
Flaccid muscles	
Diminished reflexes	
Muscle cramps (abdominal and leg)	
Lethargy	
Tingling or cramping in feet and hands	
Confusion	
Nausea and vomiting	
Shortness of breath	

Source: References 5 and 6.

Because the GI tract is the site of nutrient absorption, some patients with ostomies may experience deficiencies owing to postsurgical changes in gut anatomy. For example, iron and vitamins D₂ and D₃ are absorbed in the small intestine; riboflavin is absorbed in the upper GI tract; vitamin B₁₂ is absorbed in

the terminal ileum; phytonadione is absorbed in the proximal small intestine; menadione is absorbed in the distal small intestine; and calcium, pyridoxine, pantothenic acid, biotin, choline, inositol, carnitine, vitamins C and E, and thiamine (vitamin B₁) are absorbed in various sites within the intestinal tract (specific sites have not been identified). Vitamin A deficiency may be seen in persons with disease of the terminal ileum (e.g., Crohn's disease).

Hypophosphatemia and hypomagnesemia are seen in people with calcium deficiency caused by malabsorption. In addition, copper deficiency, which interferes with the absorption of iron, has been reported in patients who have undergone intestinal bypass surgery. Folic acid absorption requires interaction with enzymes present in the upper part of the jejunum; therefore, absorption of folic acid takes place predominantly in the proximal part of the small intestine.⁷⁻⁹

The effect of ostomy surgery on absorption of vitamins and minerals has not been well studied; however, patients with ileostomies or colostomies should be monitored for signs and symptoms of deficiencies.

Patients with a urostomy, an ileostomy, or an ascending colostomy require adequate daily intake of fluid to prevent the precipitation of crystals or kidney stones in the urine. In addition, they may be at increased risk for gallbladder stone formation. Patients with a urostomy should adjust their diet to produce acidic urine, thereby reducing the risk of infection and crystal formation around the stoma. Cranberry products have been studied in the prevention of recurrent urinary tract infections. However, sufficient evidence to support its use in all patient populations is conflicting across various studies.¹⁰⁻¹³

Considerations in evaluating these studies include patient population, product used (especially the percentage of the active ingredient), drug-drug interactions, recurrent infections versus prophylaxis, and trial methodology.

Systemic Complications

Constipation is caused by the regular use of opioid-containing analgesics or may be a result of the patient's eating habits (e.g., insufficient dietary fiber, fluid intake). Constipation may be a problem in patients with descending and sigmoid colostomies. Treatment depends on the cause and may include dietary changes or medication adjustment. Patients experiencing problems with constipation should be encouraged to avoid the foods listed in [Table 22-3](#) that can thicken the stool.^{5,6}

Certain foods can cause diarrhea in ostomy patients ([Table 22–3](#)).^{5,6} Gut pathology (e.g., ulcerative colitis, Crohn’s disease, *Clostridioides difficile* colitis), or obstruction caused by a food bolus also can cause diarrhea. Medications, influenza, and food poisoning are other potential causes. Diarrhea is a special problem in patients with ileostomies and ascending colostomies because the associated bowel changes cause impaired fluid and electrolyte reabsorption. Patients with chronically loose stools may wish to use an absorptive agent (e.g., Ileosorb, Par-Sorb) designed for placement in the pouch. Absorptive agents do not correct the problem; they merely assist in coping with the problem. Increased nonfermentable fiber (e.g., Metamucil, Citrucel) may be used to help correct diarrhea in patients with a colon. Antidiarrheals (e.g., loperamide, diphenoxylate plus atropine) can slow transit time and decrease output. Of note, an unexpected high or decreased output or no output in a patient with an ileostomy may reflect a partial small-bowel obstruction. In such instances, the patient needs to seek emergency medical attention.

Intestinal gas is another potential problem that may be related to food. Eliminating foods that cause gas formation from the diet may be adequate to correct the problem ([Table 22–3](#)). Oral simethicone to reduce gas production or use of pouches with gas filters may be helpful. Odor is not normal except when the pouching system is changed or emptied. Otherwise, odor may be an indication of poor hygiene, leakage, or failure to properly connect the pouch to the skin barrier. The health care provider should review proper care and connection of the pouching system with patients who are concerned about odor. Oral deodorants that will act in the digestive system to eliminate odors from digested foods are discussed in the earlier section on deodorizers.

Peristomal Skin Complications

Peristomal skin complications are defined as skin inflammation, injury, or damage that occurs within the 3–4 inches of skin surface surrounding the stoma or that involves the skin covered by the adhesive portion of the pouching system (barrier and tape).¹⁴ The most common cause of peristomal skin complications is peristomal moisture-associated damage, often resulting from exposure of the skin to stoma effluent. Peristomal skin complications are reported to be as high as 77%.^{15,16}

Skin irritation around the stoma can result from prolonged contact with stoma effluent. Ostomy pouching systems and accessories also can irritate skin as a

consequence of poor fit or the irritative nature of materials used in their composition. The peristomal skin may look “weepy” or erythematous, with papules and macules evident. Several peristomal skin assessment tools are available for both clinician and patient: The Ostomy Skin Tool (OST) ¹⁷ and the Peristomal Skin Assessment Guide¹⁸ are two tools for the clinician, and the Consumer Peristomal Skin Assessment Tool¹⁹ is for the person with an ostomy.

Peristomal moisture-associated skin damage is the most commonly reported skin complication for the patient with a urinary or fecal diversion. Peristomal moisture-associated skin damage is defined as inflammation and erosion of the skin adjacent to the stoma associated with exposure of the effluent such as urine or stool.²⁰ The injured area appears red, with superficial skin loss, and the changes observed can mirror the pattern of exposure of the skin to the stoma output. Management of the injured skin includes identification and correction of the contributing factors, which may include the opening in the skin barrier differs from the size or shape of the stoma, the shape of the pouching system does not match that of the peristomal area, prolonged wear time, or user error. Once the etiologic condition has been determined and corrected, a skin barrier powder may be applied to the peristomal skin before the pouch is applied (see earlier).

Allergic contact dermatitis is characterized by burning, pruritus (itching), blisters, and red or denuded skin. This complication usually results from an allergic reaction to the pouching system or an accessory. The area of involvement usually matches the contour of the product causing the reaction. A patch test will identify the allergen in patients who have a history of allergy or of reaction to adhesive tape, eczema, or psoriasis, as well as in those who have very fair skin. Management includes identifying and removing the allergen. It may take some time for the redness to dissipate, and a topical corticosteroid spray can be used to decrease the inflammation. For persons at risk for such reactions, “patch testing” a variety of products is an option to determine if they will be tolerated without problems.

Pseudoverrucous lesions (encrustations) may develop in patients with urinary diversions because of the alkalinity of the urine. With continuous contact of this abnormal urine with the skin, an alkaline dermatitis will result, manifested as thickening of the affected skin with gray discoloration due to deposition of alkaline crystals. The first step in management is to prevent any urine contact with the skin, so a new pouching system, a refitting of the skin barrier opening,

or a decrease in the wear time may be needed. A cloth soaked with a solution of one-third white vinegar to two-thirds water should be applied to the involved area for 5–10 minutes at pouch change to help to dissolve the crystals. Definitive treatment for alkaline dermatitis is acidification of the urine. Patients should avoid alkaline ash foods, such as citrus fruits and juices; paradoxically, these foods are acidic when consumed but generate an alkaline output. Increasing fluid intake to 2–3 quarts daily also may reduce alkalinity. Acidifying the urine with cranberry juice or pills may be considered as well.

Mechanical injury may result from a variety of causes; most common are medical adhesive–related skin injuries and pressure injuries. Medical adhesive–related skin injuries occur on removal of the pouching system. The area of injury is located specifically beneath the adhesive portion of the pouching system; the injury lesion, which is moist and typically painful, manifests as a partial thickness skin loss. Some cases are preventable such as with gentle adhesive removal (by the push-pull method) or the use of an adhesive releaser or remover. The injured skin can be treated with skin barrier powder to provide a dry surface to heal the skin. If the affected area is extensive, a thin hydrocolloid dressing can be used until healing occurs. Pressure injuries can develop in the peristomal area and manifest as full or partial thickness lesions in an area under pressure from the pouching system, such as a convex skin barrier or the inappropriate use of a belt. Treatment for the pressure injury begins with identifying the part of the pouching system causing the prolonged pressure, with appropriate modifications to correct the problem, followed by specific measures to help heal the injury, such as application of a thin hydrocolloid or superficial skin barrier powder.

Folliculitis, an inflammation of the hair follicles, is characterized by redness at the base of the hair follicles around the stoma. Aggressive removal of any adhesive from the skin can traumatically remove hairs, resulting in irritation and infection. Using a clipper to remove hair in the peristomal area may help prevent folliculitis. Because folliculitis is related to an overgrowth of staphylococci on the skin, the use of an antibacterial wash should be considered; in some advanced cases, use of an oral antibiotic may be considered.

Fungal infection/candidiasis can develop in the peristomal area in patients who are on antibiotics, are immunosuppressed, have diabetes, or are undergoing chemotherapy. Candidiasis manifests with pruritus and

maculopapular rash with satellite lesions. The moisture associated with the rash can interfere with the pouch seal causing leakage. Treatment of the condition is with the use of the powdered antifungal agent nystatin. As with skin barrier powder, the powder can be liberally applied to the affected area and rubbed in, and the excess brushed off. Once the area clears, the powder is no longer necessary.

Stoma Complications

Stoma stenosis is narrowing or contraction of the stomal tissue at the skin or fascial level. Causes are thought to be related to postoperative ischemia, active disease such as Crohn's disease, or excessive scar formation. Management of mild stenosis may include a low-residue diet and use of stool softeners. For severe stoma stenosis, stoma revision should be considered.

Peristomal hernia is a defect in the abdominal wall that allows the intestine to bulge into the peristomal area and is one of the most common ostomy complications. Several risk factors for development of a peristomal hernia have been suggested: creation of a large fascial opening, placing the stoma lateral to the rectus sheath, obesity, and malnutrition. The patient may complain of a bulge when standing or sitting, pain, pouching difficulties, leakage, and peristomal skin irritation. Modification of the pouching system to a more flexible system to fit over and around the peristomal bulge may help with the pouch seal. An ostomy support belt or binder may be used to provide comfort and reduce the bulge. The patient should be referred to a WOC nurse for a plan of care. Surgery may be required if pain at the site increases, the degree of herniation worsens, or signs of stoma obstruction develop.

Fistula is an abnormal opening between two internal organs, or from inside the body extending through the skin. Enterocutaneous fistulas (abnormal passages between the intestine and skin) can occur in patients with or without an ostomy. This complication is most often a manifestation of Crohn's disease, advancing cancer, abscess formation, radiation damage, and traumatic injury. If a fistula exhibits excessive drainage, an ostomy pouching system may be applied to contain the effluent, which otherwise can induce skin damage with denudation.

Prolapse is a telescoping of the intestine through the stoma. This pathoanatomic problem is thought to result for a number of reasons: too-large

opening in the abdominal wall, inadequate surgical fixation of the bowel to the abdominal wall, or poorly developed fascial support. The danger of prolapse is in the resulting decrease in blood supply to the bowel present outside the abdominal cavity. The enlarged stomal protrusion is more susceptible to damage from the pouching system and is frightening to the patient. Treatment usually is conservative. The prolapse may be reduced by having the patient lie supine and applying continuous pressure on the most distal part of the stoma. Placement of cold packs on the stomal area may reduce the associated edema, facilitating reduction of the prolapse. Once reduction is obtained, use of a rigid pouching system should be avoided because of the risk of strangulation of the stomal tissue. The patient should apply a flexible pouch with a resized opening while lying flat. Surgical correction may be required if the stomal tissue becomes purple or ecchymotic or if the prolapse persists.

Retraction is the disappearance of stoma tissue to below skin level. Causes include tension on the stoma from a variety of reasons such as a short mesentery, thickened abdominal wall, obesity, and stomal necrosis. If the retraction is not severe, use of a convex pouching system and a belt may be adequate. In other cases, surgical correction may be required.

Medication Considerations With Ostomies

An understanding of the absorption characteristics of medications is important to optimize their effectiveness in patients with ostomies. Both prescription and nonprescription medications should be reviewed to ascertain the best formulation for each patient. Potential drug interactions and adverse effects of special concern in patients with ostomies also should be addressed in the drug therapy plan. [Table 22–8](#) lists some general drug management principles for patients with colostomies, ileostomies, and urostomies.^{21,22}

Table 22–8 General Drug Management Principles With Ostomies

Type of Ostomy	General Management
Ileostomy, colostomy	Avoid sustained-release, extended-release, and enteric-coated medications or those that contain a wax matrix. Liquid, crushable, and chewable preparations are preferred.
Ileostomy, colostomy	Do not crush medications before first consulting an appropriate health care provider.

Type of Ostomy	General Management
Ileostomy, colostomy	Check pouch for undissolved tablets to monitor drug absorption.
Ileostomy, colostomy, urostomy	Review medication plans for potential drug interactions and/or adverse effects.
Ileostomy, colostomy, urostomy	Alert patients to medication-induced color changes in urine and/or stool.

Source: References 21 and 22.

Medication Absorption With Ostomies

The upper portion of the small intestine is the major absorptive site for many medications. However, many drugs rely on an intact colon for absorption.²¹ Changes in GI anatomy after ostomy surgery will therefore affect the body's handling of certain drugs, in different formulations.

Formulation Characteristics and Absorption With Ostomies

Drug absorption in the presence of an ostomy is well known to be affected by product formulation, among multiple factors (Table 22–8). Patients with ostomies should be instructed to check the pouch for undissolved tablets or tablet fragments whenever they take solid oral medications. If the absorptive areas of the intestine have been altered, coated or sustained-release preparations may pass through the intestinal tract without being absorbed, potentiating drug failure.²² Some medications also are contained within a wax matrix (e.g., Slow K) from which the active drug leaches as the tablet moves through the GI tract.

Specific Drug Classes Associated With Adverse Effects Including Malabsorption in Patients With Ostomies

In addition to the noted challenges with drug absorption, [Table 22–9](#) lists a broad selection of medications with the potential to cause adverse effects, which vary with different dosage forms.^{23–34} Presented here is an overview of such effects with commonly used drugs in patients with ostomies.

Table 22–9 Potential Effects of Selected Prescription Drugs in Patients With Ostomies

Drug Class	Type of Ostomy	Potential Effects
Histamine type 1 (H ₁) receptor antagonists	Ileostomy, colostomy, urostomy	No problems have been reported with use of cetirizine, loratadine, or fexofenadine.
Anti-inflammatory agents	Ileostomy	NSAIDs are associated with GI irritation and bleeding. Use only with caution in patients with history of GI ulceration or bleeding and in those with inflammatory bowel disease (COX-2 inhibitors may have lower risk profile).
		No problems have been reported with Celecoxib.
Opiates	Colostomy	Tramadol's opiate agonist activity can cause constipation, by a similar mechanism for opiates such as oxycodone.
		Liquids, IR products, or patches are preferred to avoid erratic absorption associated with ER products.
Selective serotonin reuptake inhibitors	Ileostomy	No problems have been reported with use of sertraline, citalopram, or fluoxetine.
		Hyponatremia and diarrhea have been reported with paroxetine, necessitating close monitoring of fluid and electrolyte status.
Antipsychotics	Colostomy, ileal conduit	Constipation has been reported with use of olanzapine and clozapine and can occur with all anticholinergic drug regimens.
		Reported delayed lithium toxicity necessitates close monitoring of serum levels in patients with ileal conduits.
Antidiabetic	Ileostomy	Possible dose-related GI effects are related to variable

Drug Class	Type of Ostomy	Potential Effects
agents		absorption of metformin, a weak base primarily absorbed in the small intestine. Some patients have experienced increased stoma output, necessitating a change in their antidiabetic regimen.
		No problems have been reported with other antidiabetic agents.
Anticonvulsants	Ileostomy	Erratic absorption has been reported with enteric-coated and SR products.
		Use of liquids or IR products is generally recommended.
Antilipidemics	Ileostomy, colostomy, urostomy	No problems have been reported with use of HMG-CoA reductase inhibitors.
Cardiac/ antihypertensive drugs	Ileostomy	Fluid and electrolyte abnormalities are common with use of diuretics.
		Careful monitoring is recommended during use of ACE inhibitors.
		Hyperkalemia may be a particular problem.
GI medications	Ileostomy, colostomy	Diarrhea is associated with use of all PPIs, necessitating careful monitoring of fluid and electrolyte status.
		No problems have been reported with use of H2RAs.
		Avoid laxatives in patients with ileostomies owing to risk of severe fluid and electrolyte disturbances.
Antimicrobial agents	Ileostomy, urostomy, colostomy	Altered normal bowel flora and diarrhea related to broad-spectrum antibiotics can be a significant problem for patients with ileostomies.
		High doses of ciprofloxacin are associated with alkaline urine; if they are used, urinary acidification to avoid bacterial overgrowth in urostomy patients requires close monitoring.
Other drugs	End-jejunostomy, ileostomy	Some reports of drug failure are associated with malabsorption of warfarin in patients with short-bowel syndrome.

Drug Class	Type of Ostomy	Potential Effects
		Adequate length of functionally intact proximal small bowel is important in cyclosporine dosing; if liquid formulation or IV administration is required, more frequent monitoring is recommended.
		Variable volume of distribution and increased clearance of gentamicin have been reported in patients with ileostomies, possibly necessitating more frequent monitoring.
		Highly variable bioavailability of digoxin (dependent on length of remaining bowel) requires monitoring for drug failure.

Key: ACE = Angiotensin-converting enzyme; COX-2 = cyclooxygenase-2; ER = extended-release; GI = gastrointestinal; HMG-CoA = hydroxymethylglutaryl coenzyme A; H2RAs = histamine type 2 receptor antagonists; IR = immediate-release; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor; SR = sustained-release.

Source: References 23–34.

Antibiotics

In general, antibiotics may alter the normal flora of the intestinal tract, causing diarrhea or predisposing the patient to development of fungal infection of the skin surrounding the stoma.

Sulfa Drugs

Use of sulfa drugs in patients with ostomies warrants attention to hydration status, because crystallization in the kidney occurs more often in the setting of fluid imbalance. To minimize this problem, an increase in fluid intake is indicated.

Diuretics

Diuretics can increase the amount of fluids and electrolytes lost through urostomies. Their use in patients with ileostomies presents a challenge because fluid losses initially are often difficult to manage. Caution is therefore

warranted with use of medications in this drug class. Frequent monitoring of fluid balance and serum electrolytes is required.

Laxatives

Because of the risk of electrolyte imbalance and dehydration, ileostomy patients should never use laxatives unless these agents have been prescribed by their primary care provider. Patients with colostomies may use laxatives, but only under close supervision. If constipation is an issue, the primary care provider may recommend a stool softener.

Antacids

Products that contain calcium may promote stone formation in patients with urostomies. Magnesium-based products can cause diarrhea in patients with ileostomies. Conversely, in patients with problems of constipation, the use of aluminum-based antacids should be avoided because of their specific association with this problem.

Opioid-Containing Products

Opioid-containing products, such as oxycodone, codeine, and morphine, decrease gastrointestinal motility, potentially causing constipation. With the high addiction potential of opioid medications and the national efforts to curb dependence on these agents, health care providers are encouraged to recommend nonopiate agents for pain management, such as acetaminophen, whenever possible. With use of opioid-containing medications, a stool softener, may be prescribed by the patient's primary care provider because of the risk of constipation.

Additional Medication-Related Issues With Ostomies

Urine and Stool Discoloration

Some medications can cause color changes in the urine and/or feces, which will be noticed more often with ostomy management. The discoloration can be unsettling to an uninformed patient, leading to unnecessary anxiety. [Table 22–10](#) lists common medications that cause such color changes.^{35–37} The

health care provider should discuss these possible changes with the patient in developing the drug therapy plan.

Table 22-10 Selected Drugs That Discolor Feces and Urine

Drugs That Discolor Feces			
Black	Fluorouracil	Blue	Orange-Brown
Acetazolamide	Hydralazine	Chloramphenicol	Rifabutin
Aluminum hydroxide	Iodide-containing drugs	Manganese dioxide	Pink-Red
Aminophylline	Iron	Methylene blue	Anticoagulants ^a
Amphetamine	Levodopa	Gray	Aspirin
Amphotericin B ^a	Melphalan	Colchicine	Barium
Anticoagulants ^a	Methotrexate	Green	Cefdinir ^b
Aspirin ^a	Nitrates	Indomethacin	Clofazimine
Barium	Nonsteroidal anti-inflammatory drugs ^a	Iron	Nonsteroidal anti-inflammatory drugs ^a
Bismuth	Phenylephrine	Medroxyprogesterone	Tetracycline syrup
Chloramphenicol	Potassium salts ^a	Green-Gray	White or Speckled
Chlorpropamide	Procarbazine		
Cholestyramine	Sulfonamides	Oral antibiotics	Aluminum hydroxide
Corticosteroids	Tetracycline	Orange-Red	Barium
Cyclophosphamide	Thallium	Phenazopyridine	Oral antibiotics
Cytarabine	Theophylline	Rifampin	Yellow or Yellow-Green
Ethacrynic acid	Thiotepa ^a	Rifapentine	Senna
Drugs That Discolor Urine			
Black	Dark	Purplish Red	Yellow
Ferrous salts	Aminosalicylic acid	Chlorzoxazone	Aloe

Phenacetin	Chloroquine	Red	Riboflavin
Senna	Metronidazole	Carbidopa/levodopa	Tolcapone
Blue or Green	Nitrofurantoin	Daunorubicin	Sulfasalazine
Amitriptyline	Phenacetin	Dimethylsulfoxide	Vitamin B ₁₂
Cimetidine (injection)	Primaquine	Doxorubicin	Yellow-Brown
Flutamide	Orange	Idarubicin	Cascara
Indomethacin	Chlorzoxazone	Red-Brown	Nitrofurantoin
Magnesium salicylate	Dantrolene	Aloe	Primaquine
Methocarbamol	Entacapone	Levodopa	Senna
Methylene blue	Warfarin	Phenytoin	Sulfonamides
Mitoxantrone	Orange-Red	Quinine	Yellow-Orange
Promethazine (injection)	Phenazopyridine	Warfarin	Sulfasalazine
Propofol (injection)	Rifampin	Violet	Vitamin A
Triamterene	Pink-Red	Senna	Yellow-Pink
	Phenothiazines		Cascara
	Phenytoin		Aspirin

^a Discoloration may be caused by bleeding.

^b Discoloration caused by nonabsorbable complex between cefdinir or metabolites and iron in the GI tract.

Key: GI = Gastrointestinal.

Source: References 35–37.

Dietary Supplements

Herbal products are not regulated by the U.S. Food and Drug Administration (FDA) because they are considered dietary supplements. Moreover, not all ingredients contained in a product are listed on the label. Herbal supplements can interact with medications and may cause a variety of adverse effects. Patients with ostomies who desire to use herbal agents should do so only under medical supervision.

Assessment of Patients With Ostomies: A Case-Based Approach

In most cases, ostomy surgery necessitates the use of a pouching system designed to collect the waste material normally eliminated through the bowel or bladder. Because the specific circumstances dictating the need for an ostomy and the resultant surgical outcomes are highly variable, one patient may function well with use of a particular type of pouch or accessory, whereas another may develop problems with the same products. Moreover, the patient's needs may change over time. A pouching system or accessory that previously produced ideal outcomes may no longer be appropriate because of changes in body contour caused by aging, pregnancy, weight gain or loss, or concurrent medical conditions. As the rate of obesity continues to rise, so do the challenges for health care providers in supporting the special needs of people with ostomies, for whom weight changes and obesity bring added complexity to management.

Patients scheduled for ostomy surgery often are apprehensive about how the operation will proceed, how they will manage the ostomy postoperatively, and how they will be perceived by others. Both pre- and postoperatively, the person's self-image typically is threatened, with a detrimental effect on self-esteem. Therefore, special efforts should be made during the assessment to ensure privacy, to establish a trusting relationship, and to bolster the patient's confidence in subsequent self-management.

Cases 22–1 and 22–2 illustrate assessment of two different patients with established ostomies.

Case 22–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient's stoma-related symptoms began during the summer when she was at the beach and perspired a lot.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	She has experienced pruritus (itching) and rash underneath her ileostomy appliance for the past week, and now the affected skin is becoming denuded and "weepy." Her pouch has started to leak more often. She usually wears this pouching system for 3–4 days, but now she can keep it on for only 24 hours.
c. Description of the patient's efforts to relieve the symptoms	The patient applied pectin-based powder before appliance changes, but her symptoms have not resolved.
d. Patient's identity	Alexis Jones
e. Patient's age, gender, height, and weight	32 years, female, 5 ft 6 in., 130 lb
f. Patient's occupation	Web designer
g. Patient's dietary habits	MNT diet for diabetes
h. Patient's sleep habits	n/a
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	<i>Diabetes:</i> Glucophage 500 mg twice daily <i>Asthma:</i> Flovent 220 mg 2 puffs twice daily, albuterol 2 puffs every 6 hours as needed

j. Why was the stoma created, what type of stoma, and how often is the pouch emptied, what is the consistency of the stool?	Ms. Jones underwent proctocolectomy with creation of an ileostomy 2 years ago for management of severe medically unresponsive ulcerative colitis.
k. Allergies	Aspirin
l. History of other adverse reactions to medications	None
m. Other (describe) -----	n/a
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Since the summer, Ms. Jones has developed a rash and itching. The rash appears to be caused by moisture. The patient's diabetes is a related factor.
3. Identify exclusions for self-treatment.	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer Ms. Jones to a WOC nurse. (2) Recommend application of nystatin powder to the affected area with each pouch change. (3) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Suggest that Ms. Jones contact the WOC nurse or other health care provider who manages her ostomy care, to obtain a prescription for nystatin powder. Advise that she should describe the rash, timing of onset, and her symptoms.

6. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	“Seeing a WOC nurse or your regular ostomy care provider is very important to treat this situation.”
Implement	
7. When providing a recommendation that the patient contact a health care provider to suggest the use of nystatin powder, convey accurate information to the patient or caregiver.	“Wash peristomal skin using your usual routine. Apply nystatin powder sparingly and rub into the peristomal skin. Dust off the excess powder. A protective barrier wipe, such as 3M No Sting Skin Prep, may be applied to enhance the pouch seal. Apply the pouch. Use the nystatin powder with each pouch change until 1 week after the rash has resolved. Avoid washing the stoma with soap, especially antibacterial soap. If the rash and itching continue, consult a WOC nurse or your primary care provider.”

Key: MNT = Medical nutrition therapy; n/a = not applicable; WOC = wound, ostomy, and continence.

Case 22–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient’s symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient has experienced leakage from his colostomy pouching system in the past few weeks. He has noticed redness, denuded skin, and a bulge around the stoma. Pain described as a burning sensation at the site also is distressing for the

	patient.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Since his surgery 1 year ago, the patient has gained 20 pounds. He usually changes his pouch twice a week, but now he has to change it every day and continues to have leakage and peristomal redness.
c. Description of the patient's efforts to relieve the symptoms	Patient applied skin barrier powder and skin sealant to protect his skin, but he continues to have skin irritation and leakage.
d. Patient's identity	Kevin Smith
e. Patient's age, gender, height, and weight	60 years, male, 5 ft 11 in., 175 lb
f. Patient's occupation	Retired engineer
g. Patient's dietary habits	High-fiber diet with junk food
h. Patient's sleep habits	n/a
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	<i>Allergic rhinitis:</i> Nasonex 2 spray in each nostril once daily or 1 spray in each nostril once daily
j. Why was the stoma created, what type of stoma and how often is the pouch emptied, what is the consistency of the stool?	Mr. Smith was diagnosed with rectal cancer 2 years ago, which was treated with preoperative irradiation and chemotherapy and then abdominal perineal resection with creation of a sigmoid colostomy. He has one stool per day that is semiformal. Lately he has noted crampy abdominal pain just before the stool discharges from the stoma.
k. Allergies	Latex
l. History of other adverse reactions to medications	None
m. Other (describe) -----	Mr. Smith has been nervous about family issues and has been constantly eating, which has increased his weight.
Assess	
2. Differentiate patient's	Leakage, pain, and denuded skin around his stoma are the

signs/symptoms, and correctly identify the patient's primary problem(s).	result of local changes including development of abdominal creases with weight gain and documented peristomal hernia.
3. Identify exclusions for self-treatment.	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required and share this information with the patient or caregiver.	Options include (1) Refer Mr. Smith to a WOC nurse for further assessment and treatment. (2) Recommend use of a skin barrier powder to improve the condition of the peristomal skin, followed by application of a skin sealant. (3) Recommend use of a barrier ring with pouching system. Mr. Smith should be fitted with a hernia belt, which will provide support. (4) Refer Mr. Smith to the website: http://psag-consumer.wocn.org/#home. that can help him to identify and plan care for the peristomal skin issues. (5) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Assessment of the stoma and skin indicates that a barrier ring and appropriate pouch are needed, as well as a hernia belt for support. Upon further discussion, Mr. Smith says he prefers a one-piece pouch with belt over a two-piece pouch.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"In addition to ostomy care, you will need a belt for support of the hernia. Treat skin around the stoma with a skin barrier powder, such as Stomahesive powder, and a skin sealant, such as 3M No Sting Skin Prep, before applying the pouch with barrier ring. Change the pouching system every 2 days until the peristomal skin is free of pain and is no longer denuded; then resume pouch changes twice a week."

7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	<i>Physiologic issues:</i> “Pouch leakage and denuded skin will decrease with proper follow-up with a WOC nurse or other ostomy care provider to modify your pouching technique. The bulge will be less prominent with support from a hernia support belt.” <i>Psychologic issues:</i> “Contact the local chapter of the United Ostomy Associations of America for peer support to help you improve your self-esteem and body image.” (See Table 22-1 .)
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
a. Appropriate dose and frequency of administration	See Figure 22-3 and Table 22-2 for proper pouching technique and appropriate skin accessories.
b. Maximum number of days the therapy should be employed	“Change the pouch twice a week.”
c. Product administration procedures	“Wash peristomal skin as usual. Apply thin layer of powder. Rub powder into skin and dust off any excess. Apply liquid skin barrier before applying the pouch with barrier ring.”
d. Expected time to onset of relief	“With proper skin care and use of a hernia belt for support, leakage and skin injury should decrease. You will notice a decrease in the burning sensation.”
e. Degree of relief that can be reasonably expected	“You should notice a decreased intensity of symptoms within 24 to 48 hours.”
f. Most common adverse effects	“Some ostomates have had an allergic reaction to the powder or pouch adhesive.”
g. Adverse effects that warrant medical intervention should they occur	“Consult a WOC nurse if burning, stinging, or local irritation occurs.”
h. Patient options in the	“Consult a WOC nurse or your primary care provider if leakage

event that condition worsens or persists	or burning continues after 1 week of treatment.”
i. Specific nondrug measures	“Change the pouch every 2 days until peristomal skin is clear.”
j. Solicit follow-up questions from the patient or caregiver.	“What happens if I can't lose weight, I develop more creases, and my stoma retracts more?”
Answer the patient's or caregiver's questions.	“Consult a WOC nurse. You may need another type of pouching system. In addition, because weight gain may lead to obesity, which carries significant health risks beyond ostomy-related problems, you should consult a nutritionist for a proper diet program.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Ask Mr. Smith to call you at the next pouch change to ensure that no further leakage has occurred and that the affected skin has improved. If the leakage continues, have the patient call the WOC nurse.

Key: n/a = Not applicable; WOC = wound, ostomy, and continence.

Patient Counseling for Ostomy Care

The pharmaceutical care needs of a patient with an ostomy include selection of the appropriate supplies and procurement and use of ostomy supplies. Monitoring the ostomy self-management regimen and counseling the patient and family on special needs (e.g., skin care, diet, fluid intake, drug therapy) are other important components of ostomy care.

Counseling of the person with an ostomy should be done in a sensitive and caring manner. A common postsurgical issue is disturbance in the person's self-image, with consequent damage to self-esteem; therefore, in assisting patients with ostomy needs, special care must be taken to avoid verbal or

facial expressions that might convey negative feelings regarding the necessary maintenance procedures. Peer support can be especially helpful for the ostomate population. Patients should be provided with contact information for local and national ostomy associations and a list of product manufacturers that can supply information about product use ([Table 22–1](#)). Further assistance can be obtained from a WOC nurse in the patient’s geographic area (www.wocn.org). The following self-help books also should be recommended to patients with ostomies:

- Barrie B. *Second Act*. New York, NY: Scribner; 1997.
- Benirschke R. *Alive & Kicking*. San Diego, CA: Rolf Benirschke Enterprises; 1999.
- Benirschke R. *Embracing Life*. San Diego, CA: Rolf Benirschke Enterprises; 2009.
- Benirschke R. *Great Comebacks*. San Diego, CA: Rolf Benirschke Enterprises; 2002.
- Elsagher B. *I’d Like to Buy a Bowel Please! Ostomy A to Z*. Andover, MN: Expert Publishing; 2006.
- Elsagher B. *If the Battle Is Over Why Am I Still in Uniform? Humor as a Survival Tactic to Combat Cancer*. Andover, MN: Expert Publishing; 2005.
- Kupfer B, Foley-Bolch K, Kasouf MF, et al. *Yes We Can*. Worcester, MA: Chandler House Press; 2000.
- Ruggieri P. *Colon & Rectal Cancer. A Patient’s Guide to Treatment*. Omaha, NE: Addicus Books; 2001.
- Taylor J. *Pretty Girl Blues*. PGB Publishing; 2013. Available at: <http://www.prettygirlblues.com/PurchasePGB.html>.

The person with an ostomy must adapt to many challenges in everyday life. Supporting the patient’s involvement in the various aspects of self-care and in the development of health care plans will help to alleviate much of the fear and anxiety often associated with living with an ostomy. Expression of any problems and concerns should be encouraged so that the patient’s ability to achieve self-treatment objectives can be better assessed. Health care providers or managers also should consider patients’ special needs for conditions unrelated to the ostomy. The box “Patient Education for Ostomy Care” lists specific information to provide in patient counseling.

Patient Education for Ostomy Care

The objectives of self-care for ostomies are (1) to understand how the stoma functions and to maintain an effective ostomy management regimen; (2) to identify and implement proper techniques for use of the pouching system and accessories, and to avoid complications that result from improper use; and (3) to reduce the risk of other types of complications. For most patients, carefully following the product instructions and the self-care measures listed here will help to ensure optimal therapeutic outcomes.

Pouching System Selection and Use

- Use only the type of pouching system recommended for your type of ostomy.
- If your system no longer fits well, consult your WOC nurse or primary care provider before changing to a different type of pouching system.
- Do not consider skin irritation to be inevitable; identify the cause and correct it, and treat the irritation as soon as it occurs.
- If possible, identify the cause for leakage around the pouching system and correct the problem immediately. Consider using the Peristomal Skin Assessment Guide, available online (<http://psag-consumer.wocn.org/#home>). Consult your WOC nurse or primary care provider if you cannot determine the cause.
- Establish a routine for ostomy care. Keep the routine simple; use as few accessories as possible.
- Order more supplies when you have four changes left.

Effects of Medication Use

- Sustained- or extended-release medicines may undergo erratic absorption because of the altered postsurgical anatomy, which makes their effect unpredictable. These medications should be used with caution. Coated medications, as well as sustained- or extended-release medications, should not be crushed or chewed.
- Use caution when taking antibiotics and diuretics. Antibiotics can cause diarrhea or promote development of fungal infections of the skin around the stoma. Diuretics can cause dehydration or

electrolyte imbalance in people with ileostomies.

- Use caution when taking laxatives, antidiarrheals, or other medications that alter gastrointestinal motility. Laxatives can increase fecal output in people with ileostomies, whereas antidiarrheals decrease the fecal output.
- Know which medications will discolor the urine or feces ([Table 22–10](#)).

When to Seek Medical Attention

- Consult your WOC nurse or primary care provider about using nonprescription medications to treat diarrhea or constipation. Seek medical attention for the problem after you experience no improvement with 1 week of self-treatment.
 - See your WOC nurse if you experience any of the following complications:
 - Depression and anxiety
 - Abdominal pain
 - Narrowing of the stoma
 - A bulge near the stoma
 - Protrusion of the bowel through the stoma
 - Retraction of stoma below the skin
 - Excessive bleeding from or around the stoma (more than a teaspoon)
 - Pain on touching the skin around the stoma or applying the pouching system
 - Overgrowth of the skin around the stoma
 - Ostomy Care

Key Points for Ostomy Care

- Patients with ostomies may experience both psychological and physical complications after ostomy surgery. Specific issues should be addressed, with referral as needed to a primary care provider, a WOC nurse, and/or the United Ostomy Associations of

America.

- The objectives of self-care for an ostomy are to understand how the stoma functions, to maintain an effective ostomy management regimen, to identify and implement optimal techniques for use of the pouching system and accessories, to avoid complications that result from improper use, and to reduce the risks of other complications.
- Patients should be advised about the effects of food on stomal output and the need to monitor for signs and symptoms of dehydration.
- The selection of an appropriate pouching system depends on the patient's stoma and body contour, manual dexterity, and type of ostomy.
- The ideal ostomy pouching system should provide a predictable wear time and protect the peristomal skin. The health care provider can assist the patient in achieving these outcomes.
- Patients should be counseled on the effects of medications:
 - Use of liquid, crushable, or chewable medications is preferable.
 - Coated or sustained-release medications require caution with use, because if the GI tract has been shortened or its function otherwise altered, full absorption may not occur.
- Caution is warranted with use of antibiotics and diuretics. Antibiotics can cause diarrhea or promote fungal infections of the skin around the stoma. Diuretics can cause dehydration or electrolyte imbalance in patients with ileostomies.
- Laxatives, antidiarrheals, and other medications that alter GI motility should be used with caution. Laxatives can increase fecal output in patients with ileostomies, whereas antidiarrheals decrease the fecal output.

Chapter 23: Essential and Conditionally Essential Nutrients

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Vitamin and mineral supplements represent one of the largest and most widely used nonprescription product categories in the United States. More than one third of Americans take a daily multivitamin/mineral (MVM) supplement; sales accounted for one sixth of all dietary supplement sales and 40% of all purchases for vitamin and mineral supplements in 2014.¹ Annual U.S. sales data for all dietary supplements in 2014 were estimated at \$36.7 billion, including \$14.3 billion for all vitamin- and mineral-containing supplements, with an estimated \$5.7 billion specifically for MVMs.¹ Use of MVM supplements has additionally increased over the past 25 years.^{2,3} Nutrition experts agree that foods are the preferred source of vitamins and minerals and that most people can easily meet their daily requirements by eating a balanced diet, although experts agree less about the extent to which the U.S. population consumes such a diet. The lack of overt symptoms of nutritional deficiency in this country supports the position that for most Americans, dietary sources provide adequate amounts of vitamins and minerals; however, the likelihood that subclinical deficiencies may contribute to chronic diseases is receiving increasing attention. Similarly, concerns have emerged that the presence of comorbid conditions and use of certain chronic medications may precipitate nutritional deficits, either by preventing adequate intake or absorption of essential nutrients (i.e., those the human body cannot make) or by creating a situation in which nutrients that are not usually essential (because of adequate endogenous production) now become essential—that is, “conditionally essential” nutrients. These concerns emphasize the importance of encouraging the selection of nutrient-dense foods throughout the life cycle and recognition of the need to recommend appropriate nutritional supplementation for persons at risk for deficiency.

According to the Dietary Supplement Health and Education Act (DSHEA) of 1994, dietary supplements, including vitamins, minerals, and MVM preparations, are not drugs and thus are not intended to prevent, cure, diagnose, treat, or mitigate disease. Health-conscious consumers, however, often seek nutritional supplements as a means of prevention and self-treatment for myriad actual or perceived health ailments; commonly cited

reasons for use are to maintain overall health and to improve health status.⁴ Marketing claims and natural product enthusiasts encourage these self-care behaviors by promoting use of nutrient supplementation, often in doses well above established tolerable upper limits.⁵ In any case, the issues of benefit versus harm from the use of nutritional supplements and the necessity of supplementation in a nutrient-replete person remain unresolved. Regular use of supplements can help in meeting recommended dietary requirements; with this approach, however, a potential risk is that some users will exceed the tolerable upper intake levels of specific nutrients.⁵ Currently, no or only limited evidence supports the use of supplements for cancer prevention; in fact, some data suggest *increased* cancer risk with intake of certain nutrients at higher doses for prolonged periods of time.^{6,7} Furthermore, the National Institutes of Health–sponsored State-of-the-Science Conference concluded that the available evidence is insufficient to support routine use of MVM supplements for primary prevention of chronic diseases.⁸

Beyond the risk of toxicity, one of the greatest dangers of “food fads,” use of multiple supplements, and “mega-dosing” with single vitamins is that such practices may be embraced as a replacement for sound medical care. The lure of marketing or the desire to self-treat may attract desperate or uninformed patients who have serious illnesses, placing them at greater risk because of the associated delay in seeking appropriate medical attention. Furthermore, drug–nutrient interactions can be significant, yet they often are overlooked as part of the patient’s medical history. For these reasons, health care providers should be aware of the potential use of various nutrient supplements, as well as their associated benefits and risks.

Epidemiology and Etiology of Nutritional Deficiencies

Although overt nutrient deficiency is rare in the United States, the prevalence of subclinical deficiencies is unknown. Specific patient populations may be at higher risk for deficient nutrient intakes because of pathophysiologic, physiologic, metabolic, behavioral, or economic factors, summarized in [Table 23–1](#).^{9,10} Beyond providing energy, protein, and other dietary essentials for day-to-day function (i.e., macronutrients), foods contain numerous other compounds that are important for health maintenance and disease prevention

(i.e., micronutrients), and health care providers can be instrumental in educating patients on choices of nutrient-dense food before vitamin and/or mineral supplementation is recommended. (See [Chapter 24](#) for further discussion of dietary components.)

Table 23–1 Factors Contributing to Nutritional Deficiency

- Inadequate dietary intake resulting from substance abuse, poverty, eating disorders, dementia, or restrictive diets
- Consumption of energy-dense but nutrient-poor foods
- Poor dentition, swallowing difficulty, or xerostomia
- Loss of taste, smell, or sight perception
- Decreased absorption resulting from malabsorptive conditions and/or surgical resection or disease of the intestine (e.g., cystic fibrosis, short bowel syndrome, Roux-en-Y gastric bypass, gastric hypochlorhydria, chronic diarrhea, inflammatory bowel disease)
- Inability to buy or prepare meals because of tremor, fatigue, or arthritic pain
- Anorexia caused by reduced physical activity, social isolation, pain, disease, or depression
- Lack of knowledge about balanced nutrition
- Increased losses, as with hemodialysis therapy
- Inadequate synthesis
- Abnormal metabolism, as with alcoholism or certain genetic polymorphisms
- Increased metabolic requirements resulting from severe injury, infection, trauma, pregnancy, or prolonged physical exercise
- Medications affecting judgment, coordination, memory, appetite, nutrient absorption, gastric pH, or gastrointestinal tract function

Pathophysiology of Nutritional Deficiencies

A comprehensive discussion of the pathophysiology of vitamin and mineral deficiencies is outside the scope of this chapter. The reader is referred to standard medical and nutrition textbooks for such information.

Clinical Presentation of Nutritional Deficiencies

A vitamin deficiency may evolve in several stages, and clinical signs may appear only after development of prolonged and significant deficiency ([Table 23–2](#)).¹⁰ Attributing clinical signs and symptoms to a single nutrient deficiency

is difficult, because in the setting of insufficiency, such manifestations may overlap, reflecting inadequacies of multiple nutrients. Signs and symptoms of specific vitamin and mineral deficiencies are reviewed for the individual micronutrients discussed later in the chapter.

Table 23–2 Stages in Evolution of Vitamin Deficiency

1. Inadequate nutrient delivery, synthesis, or absorption
2. Depletion of nutrient stores
3. Biochemical changes
4. Physical manifestations of deficiency
5. Frank morbidity and death

With its global scope of effect, poor nutrition increases the overall risks of chronic disease, infection, and complications associated with reproduction, acute illness, surgery, and chemotherapy. For the pediatric population, growth, development, and learning may be compromised. For adults, poor nutrition over a lifetime can exacerbate the aging process, causing earlier morbidity and death. Balanced nutrition (with varied food choices providing adequate protein and appropriate calories, vitamins, and minerals) is essential for health through all stages of the life cycle.

Nutrient Supplementation: Principles and Terminology

Vitamin and mineral supplements should be used as *adjuncts* to a balanced diet, not as substitutes for nutritious food. Although nutritional supplements can be obtained without a prescription and typically are self-prescribed, they are complex agents with specific indications. Medical assessment should precede their use, especially with popularized regimens of daily intakes that exceed recommended amounts for a specific nutrient. Furthermore, vitamins and minerals often are better absorbed from food sources than from supplements—a point that should be highlighted for persons seeking to purchase such supplements. Health care providers may refer patients to a registered dietitian for personalized counseling on diet modification as well as

nutritional supplementation.

Nutritional supplement use is intended to prevent nutritional deficiencies, replenish compromised nutrient stores, or maintain the present nutritional status. Nonprescription nutritional supplements are not intended for self-treatment for vitamin deficiencies.

In the United States, *Dietary Reference Intakes* (DRIs), nutrient reference standards, are established by the National Academies of Science, Engineering, and Medicine. These standards are intended to guide good nutrition by addressing the adequacy of the food supply, establishing principles and guidelines for adequate dietary intake, and providing authoritative judgment on the relationships among food intake, nutrition, and health. DRI is the general term for a set of reference values used to evaluate nutrient intakes of healthy people, outlined in [Table 23–3](#). Values vary according to the subject's age and sex and include

Table 23–3 Dietary Reference Intake (DRI) Components: Terminology and Definitions			
Component	Name	Definition	Comments
DRI ^a	Dietary Reference Intake	An assembly of 7 reference standards developed under the National Academies of Sciences, Engineering, and Medicine for planning and assessing diets relative to nutrient intake in apparently healthy people	Information presented in this table is divided into 22 categories ("groups") defined by sex and life stage (age). The reference standards are established by consensus committees.
EAR	Estimated Average Requirement	Amount of a nutrient per day that is expected to meet the requirement of 50% of healthy persons in the group	Based on a specific indicator of adequacy for the nutrient and a thorough review of the literature.
RDA	Recommended Dietary Allowance	Amount of a nutrient per day that is expected to meet the nutrient requirements for maintenance of good health in healthy persons	Based on normal distribution within an EAR; meets requirements for 97%–98% of healthy persons in the specified group.

Component	Name	Definition	Comments
		within the group; set at 2 standard deviations above the EAR	
AI	Adequate Intake	Average daily intake of a nutrient for persons in the group who appear to be healthy and maintaining a defined criterion of adequacy Inadequate scientific data, due either to lack of studies or inherent uncertainty, to establish an EAR with confidence for that nutrient	Based on experimentally derived intake levels or observations of mean nutrient intakes by the group. Mean intake is used for healthy breastfed infants; believed to meet requirements for the other groups.
UL	Tolerable Upper Intake Level	Highest usual intake of a nutrient that may be consumed daily without risk of adverse effects in healthy persons within the group Established for 19 nutrients based on current literature: vitamins A, D, E, and C, plus folate, niacin, pyridoxine (B ₆), choline, iron, calcium, magnesium, and phosphorus	Risk is assessed on toxicology data for most nutrients.
CDRR	Chronic Disease Risk Reduction Intake	Recommendation for a specific nutrient or other food substance to mitigate or reduce the risk of chronic disease based on an appropriate chronic disease endpoint A CDRR has been established only for sodium in adults 19 years and older: reduce intakes if above 2300 mg daily	A recent addition to DRIs; guiding principles for determining CDRRs were published in 2017. ^b Endpoints related to chronic disease were used to establish AIs for sodium, potassium, fluoride, and total fiber, and EARs for calcium and vitamin D; however, these are not the same as CDRR.

Component	Name	Definition	Comments
AMDR	Acceptable Macronutrient Distribution Range	Range of usual intakes for a macronutrient that provides adequate intakes of essential nutrients and is related to reduced risk of chronic disease	Expressed as a percentage of total energy intake. The reader is referred to standard nutrition textbooks for information about AMDRs; they are not discussed in this book.
EER	Estimated Energy Requirement	Energy intake calculated using weight, height, physiologic state (e.g., pregnancy, lactation), and degree of energy expenditure that is estimated to maintain energy balance or normal growth (pediatrics)	The reader is referred to standard nutrition textbooks for information about EERs; they are not discussed in this book.

^a Links to DRI-associated tables can be found at: <http://www.nationalacademies.org/hmd/Activities/Nutrition/SummaryDRIs/DRI-Tables.aspx> and http://www.nationalacademies.org/hmd/~media/Files/Report%20Files/2019/DRI-Tables-2019/6_DRIValues_Summary.pdf?la=en.

^b Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease is available at: <https://www.nap.edu/download/24828> (doi: 10.17226/24828).

- *Recommended Dietary Allowance (RDA)*: average daily level of intake sufficient to meet the nutrient requirements of nearly all healthy people
- *Adequate Intake (AI)*: established when evidence is insufficient to develop an RDA and is set at a level assumed to ensure nutritional adequacy
- *Tolerable Upper Intake Level (UL)*: maximum daily intake unlikely to cause adverse health effects

If the patient's diet is not providing micronutrients in the amounts required for normal growth and function, supplementation with vitamins and minerals may be appropriate, in the absence of any underlying pathology or contraindication. A once-daily MVM formulation providing no more than 100% of the DRIs should suffice in most cases. Patient counseling should emphasize

that for healthy people, no specific benefit is derived from supplementing nutrients in doses above the DRI; in addition, ULs for daily use should not be exceeded without medical supervision.

Another consideration in use of nutritional supplements is the potential disparity between a product's actual content and its labeled content. Such labeling inaccuracies are not uncommon, because despite U.S. regulations requiring that the actual content of a vitamin or mineral supplement be equal to or greater than the amount stated on the product label (to account for shelf life losses and differences between manufacturer product batches), dietary supplements are not assessed for compliance or standardization by any government agency.¹¹ Unlike prescription drugs, dietary supplements do not require proof of safety or efficacy before being marketed, although standards for manufacturing, packaging, and labeling have been established by the U.S. Food and Drug Administration (FDA). Additionally, third party and independent verification programs also exist, such as the United States Pharmacopoeia–Dietary Supplement Verification Program (USP-DSVP) and those from NSF International and the Natural Products Association, among others. Availability of products bearing such seals indicating validation of adherence to good manufacturing practices creates an opportunity for the pharmacist to educate patients on product selection standards and quality.¹²

Patients should be reminded that the best method for avoiding nutritional deficiencies is to consume a balanced diet each day that includes foods from sources high in several essential nutrients. To guide consumers in selecting a balanced diet while allowing for individual preferences, the U.S. Department of Health and Human Services and the U.S. Department of Agriculture together release the reference *Dietary Guidelines for Americans* every 5 years. The 2015–2020 Guidelines are current until replaced by *Dietary Guidelines for Americans, 2020–2025*.¹³ In these guidelines, consumers are advised to regularly choose a variety of nutrient-dense foods in moderate portion sizes, as exemplified in the *MyPlate* diagram (Figure 23–1). Each food group represented on *MyPlate* provides a significant source of essential nutrients. For example, the dairy group is a major source of calcium, and the fruit and vegetable groups are sources of fiber and the primary sources of antioxidant vitamins. By selecting a variety of foods within the various groups and eating the appropriate number of servings from each food group daily, consumers can “balance” the diet for adequate intake of essential and conditionally essential nutrients. *MyPlate* is an evidence-based tool that is both user-friendly and

comprehensive for assessing the need for nutrient supplementation. When performing a nutritional assessment and determining the need for multivitamin supplementation, the health care provider should inquire about the patient's intake from these food groups.¹³

Figure 23–1 Basic food groups as shown on the MyPlate diagram. (Source: Image from www.choosemyplate.gov.)

Although high doses of specific vitamins and minerals are reported to be of therapeutic benefit for certain conditions, megavitamin enthusiasts' claims have not been confirmed objectively. To the contrary, as noted earlier, some clinical trials have suggested potential harm from supplementation originally claimed to be beneficial. These results are described within the individual micronutrient sections.

Vitamins and minerals that have therapeutic value in the treatment of medical conditions (e.g., niacin therapy for hyperlipidemia) are being used as drugs rather than as supplements for disease prevention or health maintenance. Deficiency states require medical management. Furthermore, in many cases, prolonged ingestion of *megadoses*—doses in excess of daily routine recommended intake values—of vitamin and mineral supplements has not been evaluated in large-scale clinical trials for safety and efficacy. Some vitamins (e.g., vitamin A, niacin, pyridoxine) and minerals (e.g., iron, fluoride) are known to have toxic effects at high doses. Therefore, patients should be cautioned against initiating high-dose self-medication with any nutrient without proper medical supervision.

Vitamins

Vitamins are nutrients that cannot be synthesized in the body in sufficient quantities and must be obtained through the diet. With conditionally essential nutrients such as L-arginine, L-carnitine, taurine, and coenzyme Q10, endogenous production is adequate in most circumstances, but certain disorders (e.g., cardiovascular disease) can be associated with impaired biosynthesis. Under these conditions, conditionally essential nutrients may then become essential nutrients, comparable to vitamins, necessitating dietary intake to meet requirements. Vitamins are used as both dietary supplements and therapeutic agents to treat deficiencies or other pathologic

conditions.

As previously noted, DRI reference values are developed by the National Academies of Science, Engineering, and Medicine (Tables 23–4 and 23–5).^{14,15} Adjustment may be necessary with strenuous physical activity, the presence of disease, or compromise of absorption site integrity by disease or resection.

Figure 23–2 summarizes sites of nutrient absorption, although some nutrients can be absorbed at other sites particularly when absorption at the primary site is compromised. As nutritional supplements, vitamins usually are dosed at 50%–150% of DRI values. Practitioners should advise caution for use of high-dose supplements (>200% of the DRI) without medical supervision. Identified ULs are listed in Table 23–6. As therapeutic agents, vitamins should be recommended only for specific evidence-based medical indications.

Figure 23–2 Major sites of nutrient absorption. The site of absorption may be influenced by transit time through the GI tract and by disease or surgical procedures that alter GI function or anatomy. Key: FA = Fatty acids (lipids); GI = gastrointestinal; HCl = hydrochloric acid; RYGB = Roux-en-Y gastric bypass; SCFA = short-chain fatty acids.

Table 23–4 Dietary Reference Intakes (DRIs): Recommended Dietary Allowances and Adequate Intakes—Vitamins Food and Nutrition Board, Institute of Medicine—National Academies of Sciences, Engineering, and Medicine							
Life Stage Group	Vitamin A (mcg/day) ^a	Vitamin C (mg/day)	Vitamin D (mcg/day) ^{b,c}	Vitamin E (mg/day) ^d	Vitamin K (mcg/day)	Thiamine (mg/day)	Riboflavin (mg/day)
Infants							
Infants 0–6 months	400*	40*	10 ^e	4*	2.0*	0.2*	0.3*
6–12 months	400*	40*	10 ^e	4*	2.0*	0.2*	0.3*
Children							
Children 1–3 years	300	15	15	6	30*	0.5	0.5
1–3 years	300	15	15	6	30*	0.5	0.5
4–8 years	400	25	15	7	55*	0.6	0.6

Life Stage Group	Vitamin A (mcg/day) ^a	Vitamin C (mg/day)	Vitamin D(mcg/day) ^{b,c}	Vitamin E (mg/day) ^d	Vitamin K (mcg/day)	Thiamine (mg/day)	Riboflavin (mg/day)
Male less than 1 year	400	25	15	7	55*	0.6	0.6
Male 1-3 years	600	45	600	11	60*	0.9	0.9
Male 4-18 years	900	45	600	15	60*	0.9	0.9
Male 19-30 years	900	90	15	15	75* 120*	1.2	1.3
Male 31-50 years	900	90	15	15	120*	1.2	1.3
Male 51-70 years	900	90	15	15	120*	1.2	1.3
Male 71 years and older	900	90	15	15	120*	1.2	1.3
Female less than 1 year	400	25	15	7	55*	0.6	0.6
Female 1-3 years	600	45	600	11	60*	0.9	0.9
Female 4-18 years	900	45	600	15	60*	0.9	0.9
Female 19-30 years	700	65	15	15	75* 90*	1.0 1.1	1.0 1.1
Female 31-50 years	700	75	15	15	90*	1.1	1.1
Female 51-70 years	700	75	15	15	90*	1.1	1.1
Female 71 years and older	700	75	15	15	90*	1.1	1.1
Pregnancy	700	75	20	15	90*	1.1	1.1
Lactation	750	80	15	15	75*	1.4	1.4
Female 19-30 years	750	80	15	15	75* 90*	1.4	1.4
Female 31-50 years	770	85	15	15	90*	1.4	1.4
Female 51-70 years	770	85	15	15	90*	1.4	1.4
Female 71 years and older	770	85	15	15	90*	1.4	1.4

Life Stage Group	Vitamin A (mcg/day) ^a	Vitamin C (mg/day)	Vitamin D(mcg/day) ^{b,c}	Vitamin E (mg/day) ^d	Vitamin K (mcg/day)	Thiamine (mg/day)	Riboflavin (mg/day)
Lactation	770	85	15	15	90*	1.4	1.4
14–18 years	1200	115	15	19	75*	1.4	1.6
Lactation							
19–30 years	1300	120	15	19	90*	1.4	1.6
14–18 years	1200	115	15	19	75*	1.4	1.6
19–30 years	1300	120	15	19	90*	1.4	1.6
31–50 years	1300	120	15	19	90*	1.4	1.6
Life Stage Group	Niacin (mg/day) ^f	Vitamin B ₆ (mg/day)	Folate (mcg/day) ^g	Vitamin B ₁₂ (mcg/day)	Pantothenic Acid (mg/day)	Biotin (mcg/day)	Choline (mg/day) ^h
Life Stage Group	Niacin (mg/day) ^f	Vitamin B ₆ (mg/day)	Folate (mcg/day) ^g	Vitamin B ₁₂ (mcg/day)	Pantothenic Acid (mg/day)	Biotin (mcg/day)	Choline (mg/day) ^h
0–6 months	2*	0.1*	65*	0.4*	1.7*	5*	125*
6–12 months	2*	0.3*	80*	0.5*	1.8*	6*	125*
Children	4*	0.3*	80*	0.5*	1.8*	6*	150*
1–3 years	6	0.5	150	0.9	2*	8*	200*
Children							
4–8 years	8	0.6	200	1.2	3*	12*	250*
1–3 years	6	0.5	150	0.9	2*	8*	200*
Males							
4–8 years	8	0.6	200	1.2	3*	12*	250*
9–13 years	12	1.0	300	1.8	4*	20*	375*
Males							
14–18 years	16	1.3	400	2.4	5*	25*	550*
9–13 years	12	1.0	300	1.8	4*	20*	375*
19–30 years	16	1.3	400	2.4	5*	30*	550*
14–18 years	16	1.3	400	2.4	5*	25*	550*
19–30 years	16	1.3	400	2.4	5*	30*	550*
31–50 years	16	1.3	400	2.4	5*	30*	550*
51–70 years	16	1.3	400	2.4 ⁱ	5*	30*	550*

Life Stage Group	Vitamin A (mcg/day) ^a	Vitamin C (mg/day)	Vitamin D (mcg/day) ^{b,c}	Vitamin E (mg/day) ^d	Vitamin K (mcg/day)	Thiamine (mg/day)	Riboflavin (mg/day)
5-9 years	16	1.7	400	2.4ⁱ	5*	30*	550*
10-13 years	16	1.7	400	2.4ⁱ	5*	30*	550*
14-18 years	16	1.7	400	2.4ⁱ	5*	30*	550*
19-30 years	16	1.7	400	2.4ⁱ	5*	30*	550*
31-50 years	16	1.7	400	2.4ⁱ	5*	30*	550*
51-70 years	16	1.7	400	2.4ⁱ	5*	30*	550*
>70 years	16	1.7	400	2.4ⁱ	5*	30*	550*
Females							
>70 years	16	1.7	400	2.4ⁱ	5*	30*	550*
19-30 years	12	1.0	300	1.8	4*	20*	375*
31-50 years	12	1.0	300	1.8	4*	20*	375*
51-70 years	12	1.0	300	1.8	4*	20*	375*
>70 years	12	1.0	300	1.8	4*	20*	375*
Females							
14-18 years	14	1.2	400ⁱ	2.4	5*	25*	400*
19-30 years	12	1.0	300	1.8	4*	20*	375*
31-50 years	14	1.3	400ⁱ	2.4	5*	30*	425*
51-70 years	14	1.3	400ⁱ	2.4	5*	30*	425*
>70 years	14	1.3	400ⁱ	2.4	5*	30*	425*
Pregnancy							
>70 years	14	1.5	400	2.4ⁱ	5*	30*	425*
14-18 years	18	1.9	600^k	2.6	6*	30*	450*
Pregnancy							
19-30 years	18	1.9	600^k	2.6	6*	30*	450*
31-50 years	18	1.9	600^k	2.6	6*	30*	450*
51-70 years	18	1.9	600^k	2.6	6*	30*	450*
>70 years	18	1.9	600^k	2.6	6*	30*	450*
Lactation							
14-18 years	17	2.0	500	2.8	7*	35*	550*
19-30 years	17	2.0	500	2.8	7*	35*	550*
31-50 years	17	2.0	500	2.8	7*	35*	550*
>70 years	17	2.0	500	2.8	7*	35*	550*

Note: This table (taken from the DRI reports; see www.nap.edu) presents recommended dietary allowances (RDAs) in **bold type** and adequate intakes (AIs) in ordinary type followed by an asterisk (*). An *RDA* is the average daily dietary intake

those who are older than 50 years to meet the folate intake by consuming foods fortified with folic acid, it is recommended that all women capable of becoming pregnant take folate 400 mcg daily from supplements or fortified foods in addition to intake of food folate. In view of evidence linking maternal folate intake with neural tube defects in the fetus, it is recommended that all women capable of becoming pregnant take folate 400 mcg daily from supplements or fortified foods in addition to intake of food folate from a varied diet until their pregnancy is confirmed and they enter prenatal care, which ordinarily occurs after the end of the periconceptional period—the critical time for formation of the neural tube. It is assumed that women will continue consuming 400 mcg from supplements or fortified food until their pregnancy is confirmed and they enter prenatal care, which ordinarily occurs after the end of the periconceptional period.

Sources: Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride (1997); Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B₆, Folate, Vitamin B₁₂, Pantothenic Acid, Biotin, and Choline (1998); Dietary Reference Sources; Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride (1997); Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B₆, Folate, Vitamin B₁₂, Pantothenic Acid, Biotin, and Choline (1998); Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc (2001); Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (2000); Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate (2005); and Dietary Reference Intakes for Calcium and Vitamin D (2011). These reports may be accessed at www.nap.edu.

Sources: Dietary Reference Intakes for Calcium and Vitamin D (2011). These reports may be accessed at www.nap.edu.

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Table 23–5 Dietary Reference Intakes (DRIs): Recommended Dietary Allowances and Adequate Intakes—Select Elements Food and Nutrition Board, Institute of Medicine—National Academies of Sciences, Engineering, and Medicine						
Life Stage Group	Calcium(mg/day)	Chromium(mcg/day)	Copper(mcg/day)	Fluoride(mg/day)	Iodine(mcg/day)	Iron(mg/day)
Infants						
Infants 0–6 months	200 ^a	0.2*	200*	0.01*	110*	0.27*
Infants 6–12 months	260 ^a	5.5*	220*	0.5*	130*	11
Children						

Children	700	11*	340	0.7*	90	7
4-5 years	1000	15*	440	0.7*	90	10
Male	1000	15*	440	1*	90	10
Male	1300	25*	700	2*	120	8
9-18 years	1300	25*	890	2*	120	8
19-30 years	1300	35*	890	3*	150	11
19-30 years	1000	35*	900	4*	150	8
31-50 years	1000	35*	900	4*	150	8
31-50 years	1000	35*	900	4*	150	8
51-70 years	1000	35*	900	4*	150	8
51-70 years	1000	30*	900	4*	150	8
70+ years	1000	30*	900	4*	150	8
Female	1200	30*	900	4*	150	8
Female	1300	21*	700	2*	120	8
9-18 years	1300	24*	890	2*	120	15
19-30 years	1300	24*	890	3*	150	15
19-30 years	1000	25*	900	3*	150	18
31-50 years	1000	25*	900	3*	150	18
31-50 years	1000	25*	900	3*	150	18
51-70 years	1000	25*	900	3*	150	18
51-70 years	1200	20*	900	3*	150	8
70+ years	1200	20*	900	3*	150	8
Pregnancy	1200	20*	900	3*	150	8
Pregnancy	1300*	29*	1000	3*	220	27
19-30 years	1300*	29*	1000	3*	220	27
19-30 years	1000*	30*	1000	3*	220	27
31-50 years	1000*	30*	1000	3*	220	27
31-50 years	1000*	30*	1000	3*	220	27
Lactation						

years	1300*	44*	1300	3*	290	10
19-30 years	1000*	45*	1300	3*	290	9
14-18 years	1300*	44*	1300	3*	290	10
31-50 years	1000*	45*	1300	3*	290	9
51-70 years	1000*	45*	1300	3*	290	9
Life Stage Group	Magnesium (mg/day)	Manganese (mg/day)	Molybdenum (mcg/day)	Phosphorus (mg/day)	Selenium (mcg/day)	Zinc(mg/day)
Infants	Magnesium (mg/day)	Manganese (mg/day)	Molybdenum (mcg/day)	Phosphorus (mg/day)	Selenium (mcg/day)	Zinc(mg/day)
Group 0-6 months	30*	0.003*	2*	100*	15*	2*
Infants 6-12 months	75*	0.6*	3*	275*	20*	3
Children 1-5 years	80	0.6* 1.2*	17	275* 460	20* 20	3 3
Children 6-12 years	130	1.5*	22	500	30	5
Male 13 years	80	1.2*	17	460	20	3
9-13 years	240	1.9*	34	1250	40	8
Male 14-18 years	410	2.2*	43	1250	55	11
31-50 years	420	2.3*	45	700	55	11
51-70 years	420	2.3*	45	700	55	11
71-80 years	420	2.3*	45	700	55	11
81-90 years	420	2.3*	45	700	55	11
91-100 years	420	2.3*	45	700	55	11
Females	360	1.6*	43	1250	55	9

~~9-13 years~~	~~2600*~~	~~1200*~~	~~2.3*~~
~~14-18 years~~	~~2600*~~	~~1600*~~	~~2.9*~~
Males			
9-13 years	3400*	1500*	2.3*
14-18 years	2500*	1200*	2.3*
31-50 years	3400*	1500*	2.3*
51-70 years	3000*	1500*	2.3*
19-30 years	3400*	1500*	2.0*
~~31-50 years~~	~~3400*~~	~~1500*~~	~~1.8*~~
Females			
51-70 years	3400*	1500*	2.0*
9-13 years	2300*	1200*	2.3*
~~14-18 years~~	~~2400*~~	~~1500*~~	~~2.8*~~
19-30 years	2600*	1500*	2.3*
31-50 years	2300*	1200*	2.3*
51-70 years	2600*	1500*	2.3*
9-13 years	2300*	1500*	2.3*
19-30 years	2600*	1500*	2.0*
~~31-50 years~~	~~2600*~~	~~1500*~~	~~1.8*~~
Pregnancy			
51-70 years	2600*	1500*	2.0*
9-13 years	2600*	1500*	2.3*
~~14-18 years~~	~~2600*~~	~~1500*~~	~~1.8*~~
Pregnancy			
31-50 years	2900*	1500*	2.3*
51-70 years	2600*	1500*	2.3*
19-30 years	2900*	1500*	2.3*
31-50 years	2500*	1500*	2.3*
51-70 years	2900*	1500*	2.3*
9-13 years	2800*	1500*	2.3*
14-18 years			

Life stage	2800*	1500*	2.3*
years			
14–18 years	2500*	1500*	2.3*
Note: This table (taken from the DRI reports; see www.nap.edu) presents recommended dietary allowances (RDAs) in bold type and adequate intakes (AIs) in ordinary type followed by an asterisk (*). An RDA is the average daily dietary intake level sufficient to meet the nutrient requirements of nearly all (97%–98%) healthy subjects in a group. It is calculated from an Estimated Average Requirement (EAR). If			

Note: This table (taken from the DRI reports; see www.nap.edu) presents recommended dietary allowances (RDAs) in **bold type** and adequate intakes (AIs) in ordinary type followed by an asterisk (*). An RDA is the average daily dietary intake level sufficient to meet the nutrient requirements of nearly all (97%–98%) healthy subjects in a group. It is calculated from an Estimated Average Requirement (EAR). If sufficient scientific evidence is not available to establish an EAR, allowing calculation of an RDA, an AI is usually developed. For healthy breastfed infants, an AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all persons in the groups, but lack of data or uncertainty in the data prevents being able to specify with confidence the percentage of persons covered by this intake. Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (2000); and Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc (2001); Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate (2005); Dietary Reference Intakes for Calcium and Vitamin D (2011); and Dietary Reference Intakes for Sodium and Potassium (2019). These reports may be accessed at www.nap.edu.

Source: Reprinted with permission from references [14](#) and [15](#).

Table 23–6 Adult Tolerable Upper Intake Levels (ULs) of Selected Micronutrients

Nutrient	Tolerable UL (mg daily)
Vitamin A	3
Vitamin D	0.1 (4000 IU daily)

Nutrient	Tolerable UL (mg daily)
Vitamin E	1000
Vitamin C	2000
Folate	1
Niacin	35
Vitamin B ₆	100
Choline	3500
Calcium	<i>9-18 years of age: 3000</i>
	<i>19-50 years of age: 2500</i>
	<i>>50 years of age: 2000</i>
Iron	45
Magnesium	350
Phosphorus	<i>9-70 years of age: 4000</i>
	<i>>70 years of age: 3000</i>
Copper	10
Fluoride	10
Iodine	1.1
Manganese	11
Molybdenum	2
Selenium	0.4
Zinc	40

Source: [Reference 14](#).

FDA has published a less comprehensive set of values to be used for food and dietary supplement labeling.¹⁶ For nutrient intakes for adults older than 18 years, values are listed as a percentage of daily values (%DV) for a 2000-calorie diet. The vitamin or mineral supplement label includes a box with the heading “Supplement Facts.” In addition to information on serving size and servings per container, the label lists all required nutrients that are present in the dietary supplement in significant amounts and the %DV, if a reference value has been established. It also lists all other dietary ingredients present in the product (including botanicals and amino acids) for which no %DV has been established. The %DV is based on DRI values for adults and for children 4 years of age and older, unless the product is designed for children younger than 4 years or for women who are pregnant or lactating.

Frequently, “natural” vitamin products are supplemented with synthetic vitamins. For example, because the amount of vitamin C present in rose hips (the fleshy fruits of a rose) is relatively small, synthetic vitamin C, which lacks the mass of vegetable matter, is added to allow product formulation as a tablet of convenient size. However, this addition may not be noted on the label, and the price of the partially natural product is often considerably higher than that for the completely synthetic—but equally effective—product. Patients should be informed that the body cannot distinguish between a vitamin molecule derived from a synthetic source and one derived from a natural source, and that most synthetic vitamins are the biochemical equivalent of the more expensive “natural” vitamins.

Fat-Soluble Vitamins

Two broad categories of vitamins exist: fat-soluble and water-soluble. Vitamins A, D, E, and K are fat-soluble vitamins. They are soluble in lipids and usually are absorbed into the lymphatic system before passing into the general circulation. Their absorption is facilitated by bile. These vitamins are stored in body tissues, so ingestion of excessive quantities may lead to toxicity. Fat-soluble vitamins, in general, come from similar dietary sources, including dietary fats and oils, milk products, and egg yolks (Table 23–7).^{13,17} Deficiencies occur when fat intake is limited or fat absorption is compromised. Diseases and conditions that may be associated with malabsorption of fat-soluble vitamins include celiac disease, cystic fibrosis, obstructive jaundice, hepatic cirrhosis, physiologic–anatomic changes secondary to bariatric surgical procedures, and short bowel syndrome. Deficiencies also may be precipitated

by drugs that affect lipid absorption, such as cholestyramine, which binds bile acids, thereby hindering lipid emulsification; orlistat, which inhibits gastric and pancreatic lipases in the intestinal lumen; and mineral oil, which is not absorbed and therefore increases fecal loss of fat-soluble vitamins. Potential drug–nutrient interactions are listed in [Table 23–8](#). The manufacturer recommends a daily multivitamin supplement for those taking orlistat; [Chapter 27](#) provides a more comprehensive discussion of the use of orlistat for weight loss.

Table 23–7 Food Sources Rich in Selected Nutrients

Vitamin	Food Sources
Fat-Soluble Vitamins	
Vitamin A	Liver, milk fat, egg yolk, yellow and dark green leafy vegetables, apricots, cantaloupe, peaches, carrots
Vitamin D	Vitamin D-supplemented milk, egg yolk, liver, salmon, tuna, sardines
Vitamin E	Wheat germ, vegetable oils, margarine, green leafy vegetables, milk fat, egg yolks, nuts
Vitamin K	Liver, vegetable oil, spinach, kale, cabbage, cauliflower
Water-Soluble Vitamins	
Vitamin C	Green and red peppers, broccoli, spinach, tomatoes, potatoes, strawberries, citrus fruit, kiwi
Vitamin B ₁₂	Liver, meat, poultry, oysters, clams, dairy products
Folate	Liver, lean beef, wheat, whole-grain cereals, eggs, fish, dry beans, lentils, green leafy vegetables, folate-supplemented cereals and grains
Niacin	Lean meats, fish, liver, poultry, grains, eggs, peanuts, milk, legumes
Pantothenic acid	Eggs, kidney, liver, salmon, yeast, some present in all foods
Vitamin B ₆	Meats, cereals, lentils, legumes, nuts, egg yolk, milk
Riboflavin	Meats, poultry, fish, dairy products, green leafy vegetables, enriched cereals and breads, eggs
Thiamin	Legumes, whole-grain and enriched cereals and breads, wheat germ, pork, beef

Vitamin	Food Sources
Biotin	Liver, egg yolk, mushrooms, peanuts, milk, most vegetables, bananas, yeast
I-Carnitine	Dairy products, meat
Choline	Egg yolk, cereal, fish, meats
Minerals	
Calcium	Dairy products, sardines, clams, oysters, turnip greens, mustard greens
Iron	Liver, meat, egg yolk, legumes, whole or enriched grains, dark green vegetables, shrimp
Magnesium	Whole-grain cereals, tofu, nuts, legumes, green vegetables
Phosphorus	Milk, meat, poultry, fish, seeds, nuts, egg yolk
Chromium	Liver, fish, clams, meats, whole-grain cereals, milk, corn oil
Cobalt	Organ meats, oysters, clams, poultry, milk, cream, cheese
Copper	Liver, shellfish, whole grains, cherries, legumes, poultry, oysters, chocolate
Manganese	Vegetables, fruits, nuts, legumes, whole-grain cereals
Molybdenum	Legumes, cereals, dark green leafy vegetables, organ meats, milk
Selenium	Meat, grains, onions, milk
Silicon	Cereal products, root vegetables
Vanadium	Shellfish, mushrooms, parsley, dill seed, black pepper
Zinc	Oysters, shellfish, liver, beef, lamb, pork, legumes, milk, wheat bran

Source: [References 13](#) and [17](#).

Table 23–8 Micronutrient–Drug and Micronutrient–Micronutrient Interactions

Micronutrient	Interacting Drug/ Micronutrient	Effect	Precautionary Measure(s)
Vitamins			

Micronutrient	Interacting Drug/ Micronutrient	Effect	Precautionary Measure(s)
Vitamins A, E (large doses)	Warfarin	Increased anticoagulation and risk of bleeding	Take only in recommended U.S. DRI amounts.
Vitamins A, E, D, K, C	Cholestyramine, colestipol, orlistat, or mineral oil	Decreased vitamin absorption	Avoid prolonged use of cholestyramine, colestipol, orlistat, or mineral oil.
Vitamin D	Phenytoin, carbamazepine, barbiturates	Increased metabolism of vitamin D	Ensure adequate dietary intake of vitamin D.
	Corticosteroids	May impair metabolism of vitamin D	Ensure adequate dietary intake of vitamin D.
Vitamin K	Broad-spectrum antibiotics (long-term therapy)	Vitamin K deficiency induced by decreased gut flora	Ensure adequate dietary intake of vitamin K.
	Warfarin	Decreased anticoagulation	Keep daily intake of vitamin K consistent.
	Vitamin E (large doses)	Antagonizes function of vitamin K	Avoid chronic supplementation with high-dose vitamin E.
	Vitamin A (large doses)	May interfere with vitamin K absorption	Avoid chronic supplementation with high-dose vitamin A.
Vitamin B ₁₂	Metformin, colchicine, anticonvulsants, ascorbic acid supplements, gastric acid-lowering agents (proton pump inhibitors, H ₂ RAs), tetracyclines, and long-term use of antibiotics	Potential decreased absorption of cyanocobalamin	Clinical significance is unknown.
Folic acid	Phenytoin and possibly other related	Possible inhibition of folic acid absorption, leading to	Monitor for megaloblastic anemia.

Micronutrient	Interacting Drug/ Micronutrient	Effect	Precautionary Measure(s)
	anticonvulsants (chronic use)	megaloblastic anemia; with subsequent increased folic acid supplementation, potential for decreased serum phenytoin levels and difficulty with seizure control	Consult with neurologist regarding supplementation, if possible. Patient should report use of any dietary supplement to their neurologist.
	Trimethoprim	Weak folic acid antagonism; decreased activity/ effectiveness; rare occurrence of megaloblastic anemia in patients with preexisting low folic acid level	Monitor for megaloblastic anemia.
	Pyrimethamine (large doses)	Possible megaloblastic anemia	Monitor for megaloblastic anemia.
	Methotrexate	Folic acid antagonism; decreased activity/ effectiveness	Monitor use of folic acid in patients on maintenance regimens for psoriasis or rheumatoid arthritis.
	Sulfasalazine	Decreased folic acid absorption when these agents are administered together	Separate dosing of these agents.
Niacin	Oral hypoglycemic agents; sulfinpyrazone and probenecid	Decreased hypoglycemic effects; possible inhibited uricosuric effects	Monitor blood glucose with regular finger sticks.
Vitamin B ₆	Isoniazid	Pyridoxine antagonism, manifested as perioral numbness resulting from peripheral neuropathy	Routinely take 50 mg daily of pyridoxine hydrochloride with isoniazid, or 10 mg of pyridoxine for each 100 mg of isoniazid.
	Phenobarbital and phenytoin	Decreased serum drug levels	Consider monitoring levels in patients

Micronutrient	Interacting Drug/ Micronutrient	Effect	Precautionary Measure(s)
			taking high-dose pyridoxine.
	Levodopa	Levodopa antagonism; decreased effectiveness	Avoid supplemental pyridoxine or, if possible, substitute levodopa/carbidopa for levodopa.
Minerals			
Calcium	Iron, zinc, magnesium	Inhibited nutrient absorption caused by high calcium intake	Separate dosing by at least 2 hours.
	Corticosteroids	Inhibited calcium absorption from gut; increased bone fractures and osteoporosis	Consider calcium supplementation.
	Aluminum-containing antacids, phosphates, cholestyramine	Decreased calcium absorption	Separate dosing by at least 2 hours.
	H2RAs, proton pump inhibitors	Decreased absorption of calcium carbonate, which requires an acidic environment	Consider calcium citrate supplementation.
	Levothyroxine	Reduced drug absorption	Separate dosing by 4 hours.
	Tetracyclines, fluoroquinolones	Decreased antibiotic absorption	Separate dosing by 2 hours.before or 6 hours.after ingestion of the antibiotic.
	Phenytoin, carbamazepine, phenobarbital	Decreased calcium absorption by increasing metabolism of vitamin D	Consider calcium and vitamin D supplementation.
Magnesium	Tetracyclines, fluoroquinolones	Decreased antibiotic absorption	Separate dosing by 2 hours.before or 6 hours.after ingestion of the antibiotic.

Micronutrient	Interacting Drug/ Micronutrient	Effect	Precautionary Measure(s)
	Levothyroxine	Reduced drug absorption	Separate dosing by 4 hours.
Phosphorus	Sucralfate or antacids containing magnesium, calcium, or aluminum	Decreased absorption of phosphorus	Ensure adequate intake of dietary phosphorus.
Iron	Antacids	Decreased iron solubility and absorption	Separate dosing by at least 2 hours.
	Tetracyclines, fluoroquinolones	Decreased antibiotic and iron absorption	If concurrent administration is medically necessary, take tetracycline or fluoroquinolone 2 hours before or 6 hours after taking iron.
	Levothyroxine	Decreased drug absorption	Separate dosing by 4 hours.
Trace Elements			
Copper	Zinc, high-dose vitamin C	Copper antagonism	Micronutrients may compete for absorption and utilization; ensure supplements are administered in balanced doses, or monitor for signs of deficiency.
Fluoride	Magnesium, aluminum, calcium	Decreased effect and absorption of fluoride	Separate supplementation by at least 2 hours.
Iodine (potassium iodide)	Lithium salts	Possible additive hypothyroid effects	Monitor thyroid function tests.
Zinc	Copper	Possible decreased copper levels	High-dose, prolonged zinc supplementation

Micronutrient	Interacting Drug/ Micronutrient	Effect	Precautionary Measure(s)
			may require copper supplementation.
	Tetracyclines, fluoroquinolones	Possible decreased antibiotic absorption	Separate dosing by 2 hours.before or 6 hours.after ingestion of the antibiotic.

Key: DRI = Dietary Reference Intake; H2RA = histamine type 2 receptor antagonist.

Vitamin A

The designation *vitamin A* refers to a large group of compounds that includes the retinoids (e.g., retinol) and the carotenoids (e.g., alpha-carotene, beta-carotene). Biochemical changes occur in some of these compounds during absorption in the intestine to form active vitamin A. Certain other compounds (e.g., the carotenoids, lutein, lycopene) are not converted to active vitamin A but have other health-promoting properties. These compounds can be found in dark green vegetables and red, orange, or deep yellow vegetables and fruits.

In healthy adults, more than 90% of the body's supply of vitamin A is stored in the liver. Because of this generous reserve, the risk of deficiency during short-term periods of inadequate intake or fat malabsorption is minimal. Infants and young children, by contrast, are more susceptible to vitamin A deficiency because they have not established the necessary reserves.

Function. Vitamin A is essential for normal growth and reproduction, normal skeletal and tooth development, and proper functioning of most organs of the body (notably, the specialized functions of the eye involving the conjunctiva, retina, and cornea). Vitamin A is thus indicated for preventing and treating manifestations of vitamin A deficiency, such as xerophthalmia (dry eye) and nyctalopia (night blindness). Synthesis of the glycoproteins necessary to maintain normal epithelial cell mucous secretions also requires vitamin A. This mucosal barrier is vital to the body's defense against bacterial infections in the upper respiratory system.

Deficiency. Vitamin A deficiency is rare in well-nourished populations.

However, an estimated 250,000–500,000 children worldwide develop blindness each year because of vitamin A deficiency.¹⁸ Conditions such as celiac or Crohn’s disease, pancreatic disorders, cancer, tuberculosis, pneumonia, and prostate disease, as well as therapy with corticosteroids, may lead to excessive excretion of vitamin A. Fat malabsorption may impair vitamin A absorption; in the United States, vitamin A deficiency occurs more often from diseases of fat malabsorption than from malnutrition.

One of the earliest symptoms of vitamin A deficiency is night blindness.¹⁸ Other characteristic clinical findings include follicular hyperkeratosis, loss of appetite, impaired taste and smell, and disturbance of equilibrium. Some of these abnormalities may be masked by those associated with concurrent deficiencies of other nutrients. The drying and hyperkeratinization of the skin caused by the disruption of vitamin A–dependent epithelial integrity predispose patients to infections.

Dosing and Daily Requirements. Vitamin A is indicated for use in the treatment and prevention of vitamin A deficiency.¹⁹ The patient’s estimated dietary intake of vitamin A is needed to determine a nontoxic dose for supplementation.

The DRI values for vitamin A are measured in micrograms as retinol activity equivalents (RAEs), for which dosing considerations are summarized in [Table 23–9](#).¹⁴ The Food and Nutrition Board recommends use of RAEs as a way to determine the amounts of carotenoids absorbed, as well as their degree of conversion to vitamin A in the body. RAEs replace the former designation of retinol equivalents (REs) used to calculate total vitamin A values from various dietary sources.

Table 23–9 Retinol Activity Equivalent Dosing Considerations	
1 retinol activity equivalent (RAE)	= 1 retinol equivalent (RE) ^a
	= 1 mcg retinol
	= 12 mcg beta-carotene
	= 24 mcg alpha-carotene
	= 24 mcg beta-cryptoxanthin
	= 3.33 IU vitamin A activity from retinol

	= 10 IU vitamin A activity from beta-carotene

^a The RAE unit has replaced the RE unit.

The DRI values for vitamin A are listed in [Table 23–4](#).¹⁴ The UL of 3 mg vitamin A daily in adults has been established on the basis of congenital birth defect risks and liver abnormalities associated with vitamin A toxicity.¹⁴ Evidence suggests high-dose vitamin A intake, even that below the established UL, may be associated with an increased risk of bone fractures.²⁰

Clearly, if the health care provider determines that vitamin A supplementation is appropriate, a nonprescription multivitamin containing no more than the DRI value of vitamin A can be recommended for self-care until the patient can be fully evaluated; under medical supervision, doses may be considerably higher.¹⁴ Preferably, a significant percentage of total vitamin A content should be contributed by beta-carotene, which is not associated with the risk of fractures or vitamin A toxicity. Beta-carotene's better safety profile may be related to limitations in its absorption and conversion to retinol.²⁰ However, the increased cancer risk associated with beta-carotene supplementation in both smokers and former smokers should be kept in mind (see under "Safety Considerations," next). High-dose vitamin A or beta-carotene therapy should never be undertaken without close medical supervision.

Safety Considerations. Because vitamin A is stored in the body, high doses can lead to a toxic syndrome known as hypervitaminosis A. The potential for development of this condition increases as patients consume multiple sources containing vitamin A: a multivitamin for eye health, another for cancer prevention, and potentially two more for treatment of skin disorders and wound healing. Long-term administration of vitamin A is unlikely to cause toxicity with doses less than 10,000 IU per day of retinol or equivalents; however, the risk for toxicity may increase in patients with chronic renal or liver disease, and in persons with low body weight, protein malnutrition, excessive alcohol consumption, or vitamin C deficiency.¹⁹ Headache is a predominant symptom and may be accompanied by diplopia (double vision), nausea, vomiting, vertigo, fatigue, or drowsiness. Treatment consists of discontinuing vitamin A supplementation, which should result in complete recovery.

Although beta-carotene toxicity is not likely, consuming large amounts of carrots in the daily diet may result in carotenemia, which can produce a yellow skin hue. Pregnant women or women of childbearing age should avoid vitamin A doses above the DRI, and the total vitamin A content of all dietary supplements and fortified foods consumed regularly should be carefully evaluated because of the teratogenic risk with excess vitamin A intake. For this reason, women of childbearing age should be reminded not to take other dietary supplements when a prescription prenatal vitamin is dispensed.

The potential role of vitamin A as a cancer-preventing antioxidant prompted two large randomized controlled trials to evaluate supplementation in current or former smokers at risk for development of lung cancer. In these trials, either no benefit with supplementation or a greater risk of lung cancer, cardiovascular disease, or death in those receiving supplementation was identified.^{21,22} Such trials confirm that vitamin supplementation cannot confer the same health benefits as those provided by a diet rich in fruits and vegetables.

Vitamin D (Calciferol)

A number of chemical compounds are associated with vitamin D activity. Cholecalciferol (vitamin D₃) is the naturally occurring form of vitamin D that is synthesized in the skin from endogenous or dietary cholesterol on exposure to ultraviolet radiation (sunlight). Ergocalciferol (vitamin D₂), which is used as a food additive, differs only slightly in structure from cholecalciferol. Metabolic activation of vitamin D requires hydroxylation by both the liver and the kidneys. The metabolite 25-hydroxycholecalciferol (calcidiol) is formed by the liver and then hydroxylated by the kidneys to its active form, 1,25-dihydroxycholecalciferol (calcitriol). Therefore, either renal or hepatic dysfunction may result in clinical manifestations of vitamin D deficiency, including hypocalcemia unresponsive to nonprescription vitamin D supplementation. Affected patients require a hydroxylated vitamin D preparation available only by prescription.

Function. Vitamin D, which has properties of both a hormone and a vitamin, is necessary for the proper formation of bone and for mineral homeostasis. It is closely involved with the activity of parathyroid hormone, phosphate, and calcitonin in maintaining homeostasis of serum calcium levels. Adequate vitamin D intake and supplementation in conjunction with sufficient intake of

calcium, not vitamin D alone, may reduce the risk of bone fractures and falls in postmenopausal women with osteoporosis when dosed according to clinical evidence.^{23,24} Other nonskeletal effects (e.g., reduced overall mortality, decreased risk for diabetes and cancer, lower rates of correlation with multiple sclerosis and allergies and asthma) have been evaluated in controlled clinical trials, with variable results.²⁵ Observational data have suggested that vitamin D deficiency may be associated with increased risk of cardiovascular diseases, including hypertension, coronary artery disease, and cardiomyopathy.²⁶ A recent meta-analysis of prospective randomized clinical data, however, suggests that supplementation with vitamin D does not confer cardiovascular disease protection or benefit.²⁷ Furthermore, high-dose vitamin D supplementation in a prospective, multicenter placebo-controlled study, the Vitamin D and Omega-3 Trial (VITAL), with patients randomly assigned to receive high-dose vitamin D (2000 IU per day, $n = 12,927$) or placebo ($n = 12,944$), did not reduce the risk of major cardiovascular events or rates of invasive cancer types, including breast, prostate, and colorectal cancer.²⁸ Caution against excess supplementation is warranted because some people may be at inherently greater risk for breast, esophageal, prostate, and pancreatic cancers.²⁵ Additional controlled trials are needed to confirm the health benefits, risks, and role of vitamin D supplementation for specific patient populations. Furthermore, as data on vitamin D supplementation and the role of serum level monitoring continue to accrue, dosing recommendations for prescription-only vitamin D formulations may be considerably higher when based on serum monitoring.

Deficiency. Vitamin D deficiency may result from inadequate intake; gastrointestinal (GI) diseases (e.g., hepatobiliary disease, malabsorption, chronic pancreatitis); chronic renal failure; inadequate sunlight exposure or dark skin pigmentation; hereditary disorders of vitamin D metabolism; obesity or gastric bypass therapy; or long-term therapy with antiepileptic medications (e.g., phenytoin, carbamazepine, primidone). In older patients, aging skin may not synthesize vitamin D efficiently, and the converting process that takes place in the liver and kidneys also may be compromised. The altered physiologic actions—in addition to reduced sun exposure, absorption, and dietary intake of vitamin D typical for this age group—leave older adults at increased risk for vitamin D deficiency.

The signs and symptoms of vitamin D deficiency are reflected as calcium abnormalities, specifically those involved with bone formation. Vitamin D

deficiency also has been associated with muscle weakness, an increased risk of falls, an increased risk of cardiovascular disease and certain cancers, and psychiatric disorders.²⁸ Of note, however, an “association” does not indicate causation, so the significance of such reported correlations remains unclear.

The classic vitamin D deficiency state is rickets, affecting children; osteoporosis with increased risk of fractures also occurs in adults. Vitamin D increases calcium and phosphate absorption from the small intestine, mobilizes calcium from bone, permits normal bone mineralization, improves renal reabsorption of calcium, and maintains serum calcium and phosphorus levels. As serum calcium levels fall, compensatory mechanisms (e.g., increased secretion of parathyroid hormone) become activated in an attempt to restore serum calcium homeostasis. Long-term increases in parathyroid hormone secretion ultimately lead to secondary hyperparathyroidism. If physiologic mechanisms fail to make the appropriate adjustments in calcium and phosphorus levels, demineralization of bone ensues to maintain essential plasma calcium levels. During growth, the demineralization process leads to a failure of bone matrix mineralization, widening of the epiphyseal plate from weight load on softened bone structures, and deformity of joints. In adults, such demineralization may lead to severe osteomalacia.

The incidence of rickets in the United States is low, but the condition is still seen. Rickets is most likely to occur in children who abstain from milk and in infants breastfed by mothers who receive an inadequate intake of vitamin D.

Dosing and Daily Requirements. Most people obtain the RDA or AI for vitamin D from dietary sources and from exposure to sunlight ([Table 23–4](#)). People who are regularly exposed to sunlight generally will have no dietary requirement for vitamin D. However, substantial segments of the U.S. population receive limited sunlight exposure, especially during the winter months. Regular use of broad-spectrum sunscreen is widely encouraged to prevent skin cancer, but that protection theoretically limits vitamin D synthesis in the skin and may warrant consideration of vitamin D intake from dietary sources; recent evidence has questioned the extent of the effect of sunscreen on influencing vitamin D synthesis. Milk and milk products are the major sources of dietary vitamin D in the United States, because milk is routinely supplemented with 100 IU (2.5 mcg) of vitamin D per cup.

Vitamin D is indicated for the treatment of hypocalcemia and hypophosphatemia associated with hypoparathyroidism. Prescription vitamin

D analogues (e.g., calcitriol) are approved for the treatment of secondary hyperparathyroidism in patients with chronic renal failure.¹⁹

If the health care provider determines that vitamin D supplementation is appropriate because of poor dietary intake or inadequate exposure to sunlight, a multivitamin supplement containing cholecalciferol (vitamin D₃) 15–20 mcg (600–800 IU) taken daily may be recommended. Some evidence suggests that vitamin D intake of up to 25 mcg (1000 IU) daily may have health benefits. The current UL for vitamin D is 100 mcg (4000 IU) daily, although this value may be increased in the future.¹⁴ Data gathered from the recent upswing in use of prescription-only high-dose (50,000 IU weekly) vitamin D supplements suggest that such doses are safe and necessary to achieve adequate serum concentrations. However, these high doses should not be recommended for self-care.

Safety Considerations. Taking more than the UL of vitamin D daily may lead to adverse effects, including anorexia, hypercalcemia, soft tissue calcification, kidney stones, renal failure, and increased risk of certain types of cancer.^{14,15} Patients receiving doses above the UL (e.g., those who have rickets or low serum concentrations) should be under medical supervision and closely monitored for these adverse effects.

Vitamin E (Tocopherol)

The term *vitamin E* refers to the tocopherols and the tocotrienols, compounds that occur naturally in plants.

Function. Vitamin E functions primarily as an antioxidant, protecting cellular membranes from oxidative damage or destruction. This process may be aided by selenium and vitamin C. Vitamin E also may have a role in heme biosynthesis, steroid metabolism, and collagen formation.

Vitamin E supplements, often combined with other antioxidants, have been promoted for treatment of numerous diseases (e.g., atherosclerosis, diabetes, cancer, Parkinson's disease, Alzheimer's disease). These recommendations often are based on observational studies in which regular intake of fruits and vegetables rich in antioxidants has shown beneficial effects on health maintenance and prevention of disease. However, clinical trials have suggested a lack of benefit with vitamin E supplementation in reducing the risks of multiple conditions, including cardiovascular events or mortality,

stroke, cancer, diabetes, and Alzheimer's disease.^{29–31} On the contrary, antioxidant supplementation that includes vitamin E may be associated with an increased risk of congestive heart failure in certain populations, increased risk of hemorrhagic stroke in adults, and an increased risk of fetal loss when given to prevent preeclampsia.^{31–33}

For both patients and providers, it is essential to recognize that vitamin supplementation is not necessarily benign and has not shown benefit over a well-balanced diet, especially with dosing in excess of the DRI.

Deficiency. Vitamin E deficiency is extremely rare but may occur in two patient populations: premature infants of very low birth weight and patients with disorders of fat malabsorption. For example, neurologic abnormalities responsive to supplemental vitamin E have been reported in some patients with biliary disease and cystic fibrosis. Vitamin E deficiency also has been associated with symptoms of peripheral neuropathy, intermittent claudication, muscle weakness, and hemolytic anemia.

Dosing and Daily Requirements. The RDA for vitamin E is reported as milligrams of alpha-tocopherol. One mg is equivalent to 1.49 international units (IU) of the natural vitamin or 2.22 IU of the synthetic form.¹⁴

The average diet supplies approximately 3–15 mg daily of vitamin E, so large doses in excess of the DRI are not necessary unless the patient is experiencing fat malabsorption. The FDA-approved use of vitamin E is for prevention and treatment of hemolytic anemia associated with deficiency.¹⁹

Vitamin E requirements may vary in proportion to the amount of polyunsaturated fatty acids in the diet. The polyunsaturated fatty acid content of the U.S. diet has increased, and the plant oils responsible for the increase are rich in tocopherol. The lack of evidence for deficiency at the present intake supports the current adult RDA of 15 mg daily; the UL for vitamin E is 1000 mg daily.¹⁴

Safety Considerations. Potential risks associated with vitamin E supplementation are described in the “Function” section.

Vitamin K

Phytonadione (vitamin K₁) is present in many vegetables. Menaquinone

(vitamin K₂) is a product of colonic bacterial metabolism. Menadione (vitamin K₃) is a synthetic compound that is 2–3 times more potent than the natural form of vitamin K.

Function. Vitamin K has important roles in normal physiology. It promotes the synthesis of clotting factors II, VII, IX, and X in the liver and also activates these factors, along with the anticoagulation proteins C and S. The clotting factors remain inactive in the liver in the presence of warfarin or in the absence of vitamin K. When vitamin K is administered, normal activity of the clotting factors resumes. Vitamin K also is necessary for the activation of osteocalcin, which plays a role in bone mineralization and the prevention of osteoporosis.³⁴

Deficiency. The DRI value for vitamin K is 90–120 mcg daily for adults, depending on age and gender.¹⁴ The normal gut flora synthesizes enough menaquinone to supply a significant part of the body's requirement for vitamin K. Therefore, the prevalence of deficiency among healthy, well-nourished persons is low. Interference with bile production or secretion may contribute to vitamin K deficiency, because vitamin K absorption in the small intestine requires bile. Malabsorption syndromes and bowel resections may lead to decreased vitamin K absorption. Liver disease also may cause symptoms of vitamin K deficiency if hepatic production of the prothrombin clotting factor is decreased. Other potential causes of deficiency include intestinal disease or resection and chronic, broad-spectrum antibiotic therapy. Deficiency may be evidenced by unusual bleeding and demonstrated by an elevated international normalized ratio (INR). Comparisons of lower and higher dietary intakes of vitamin K indicate increased risk of osteoporotic fractures with lower intake; however, well-designed trials are needed to confirm this association.³⁴

Dosing and Daily Requirements. The DRI values for vitamin K are listed in [Table 23–4](#); a UL for vitamin K has not been established.¹⁴ Vitamin K₁ (phytonadione) is approved for use in neonates at birth (1 dose of 1 mg) to prevent hemorrhage. This dose is necessary because placental transport of vitamin K is low, and the neonate has yet to acquire the intestinal microflora responsible for producing the vitamin. Other approved uses include the prevention and treatment of hypoprothrombinemia caused by drug-induced deficiency and the treatment of hemorrhage.¹⁹

Consistent dietary intake of vitamin K (70–140 mcg daily) does not usually interfere with warfarin anticoagulant activity. However, sudden changes in the

dietary or supplemental intake of vitamin K can significantly alter the patient's INR.

Safety Considerations. Even in large amounts over an extended period, vitamin K does not produce toxic manifestations. However, the vitamin K content of MVM products should be evaluated for anyone receiving warfarin for anticoagulation.

Water-Soluble Vitamins

Vitamin C, the B-complex vitamins (riboflavin, thiamine, B₆, B₁₂, niacin, pantothenic acid, biotin, folic acid), and the vitamin-like compound choline are classified as water-soluble vitamins. These vitamins generally are not stored in the body, and excess quantities tend to be excreted in the urine. Therefore, daily intake of these vitamins is desirable for optimal health. Thiamine, riboflavin, niacin, vitamin B₆, and pantothenic acid are involved in cellular energy production and utilization, and they may support synthesis of amino acids, fatty acids, cholesterol, steroids, and glucose.³⁵ Biotin may support fat and carbohydrate metabolism, whereas folate, vitamin B₆, vitamin B₁₂, choline, and riboflavin are involved with homocysteine metabolism; folate also is a critical cofactor in deoxyribonucleic acid (DNA) synthesis. All B-complex vitamins come from similar dietary sources ([Table 23-7](#)), so persons presenting with signs and symptoms of deficiency in one of the B-complex vitamins also may be at risk for deficiency in others. A listing of select drug–micronutrient interactions with the water-soluble vitamins is included in [Table 23-8](#).

Vitamin C (Ascorbic Acid)

Vitamin C is the most easily destroyed of all of the vitamins because of its sensitivity to heat, oxygen, and alkaline environments. It is a relatively simple compound with powerful antioxidant activity that serves to protect the capillary basement membrane. Vitamin C has been called the “fresh food” vitamin; most of the daily vitamin C intake is derived from vegetables and fruit sources.

Function. Vitamin C is necessary for the biosynthesis of hydroxyproline, a precursor of collagen, osteoid, and dentin. This vitamin also assists in the absorption of nonheme iron from food by reducing the ferric iron in the stomach to ferrous iron. However, use of vitamin C supplementation with iron

generally is not necessary for patients with normal gastric acidity who are taking adequate doses of iron.

Large doses of vitamin C (500–1000 mg daily) have been promoted to prevent and treat the common cold. Of note, such claims are largely unsupported by well-designed controlled clinical studies.^{18,36} Consumption of 5 servings or more of fruits and vegetables daily (≥ 200 mg vitamin C) has been associated with a lower incidence of cancer, heart disease, stroke, and certain eye diseases.³⁷ However, currently available data are inadequate to support vitamin C supplementation above the DRI for the prevention or treatment of these chronic conditions.³⁶

Deficiency. Characteristics of vitamin C deficiency include fatigue, capillary hemorrhages and petechiae, swollen hemorrhagic gums, and bone changes. Deficiency also may impair wound healing. Profound dietary deficiency eventually can lead to development of scurvy, with widespread capillary hemorrhaging and a weakening of collagenous structures.

Scurvy is rare in the United States because it develops only with chronically inadequate consumption of vitamin C. Infants who are fed artificial formulas without vitamin supplements may develop symptoms of scurvy. In adults, however, scurvy occurs after 3–5 months of a diet free of vitamin C.

Dosing and Daily Requirements. Health care providers are rarely confronted with patients with overt signs and symptoms of vitamin C deficiency. Only 10 mg daily of vitamin C prevents scurvy; a normal diet containing fresh fruits and vegetables contains many times this amount. The DRI values for vitamin C are listed in [Table 23–4](#). Supplementation of 100–125 mg daily has been recommended for smokers, because higher daily ascorbic acid losses were observed in such patients.³⁶ The UL for vitamin C is 2 g daily.¹⁴

Most adult multivitamin supplements contain 60–100 mg of vitamin C, an appropriate amount to consume if supplementation is required. A daily dose greater than 400 mg is rarely indicated, and excess intake is excreted in the urine. In patients with a severe vitamin C deficiency, as evidenced by clinical signs of scurvy, 100–300 mg daily of vitamin C for at least 2 weeks is recommended to replenish body stores.¹⁹ Infants who do not have vitamin C supplements in their formula should receive 40–50 mg daily; infants who are breastfed by well-nourished mothers will receive a sufficient amount. If a supplement is warranted for an adult, the health care provider may

recommend a multivitamin product containing 60–200 mg of vitamin C to be taken once a day. Vitamin C is indicated for use in the prevention and treatment of scurvy and to acidify the urine.¹⁹

Safety Considerations. With a clinical presentation indicative of vitamin C deficiency, the relative risks and benefits of ascorbic acid therapy should be considered in each case. A short-term trial of ascorbic acid with medical supervision may be warranted to promote wound healing in potentially deficient patients. Megadoses, however, may cause nausea, stomach cramps, diarrhea, and nephrolithiasis. Ascorbic acid toxicity also can lead to hemolysis in patients deficient in glucose 6-phosphate dehydrogenase. Rebound scurvy has occurred in infants whose mothers took megadoses of vitamin C during pregnancy. Vitamin C in doses of 1 g daily with 400 IU of vitamin E resulted in an increased risk of fetal loss or perinatal death when this regimen was given for prenatal supplementation.³³ Patients with diabetes mellitus, recurrent renal calculi, or renal dysfunction also should avoid prolonged use of high-dose vitamin C supplementation.

Vitamin B₁₂ (Cyanocobalamin)

Vitamin B₁₂, the most complex vitamin molecule, exists in several forms, all of which contain the element cobalt. The term *vitamin B₁₂* refers to all cobalamins that have vitamin activity in humans. Cyanocobalamin, the common pharmaceutical form of the vitamin, is the most stable of the cobalamins.

Function. Vitamin B₁₂ is active in all cells, especially those in the bone marrow, the central nervous system (CNS), and the GI tract. It also is involved in fat, protein, and carbohydrate metabolism. A cobalamin coenzyme functions in the synthesis of DNA and in the synthesis and transfer of single-carbon units (e.g., the methyl group in the synthesis of methionine and choline). Vitamin B₁₂ participates in methylation reactions and cell division, usually in concert with folic acid. Vitamin B₁₂ is necessary for the metabolism of folates; therefore, folate deficiency may be observed in concert with vitamin B₁₂ deficiency. Vitamin B₁₂ also is necessary for the metabolism of lipids and the formation of myelin.

Vitamin B₁₂ has been studied in relation to elevated levels of homocysteine, an amino acid that requires vitamins B₁₂, B₆, and folate as cofactors for

metabolism. Hyperhomocysteinemia has been identified as an independent risk factor for cardiovascular disease. Supplementation with folate, vitamin B₆, and vitamin B₁₂ has been shown to reduce plasma homocysteine levels. However, this apparent benefit has not been proved to lower the risk of major coronary or major vascular events in persons at increased risk for cardiovascular disease.³⁸

Deficiency. Vitamin B₁₂ is found almost exclusively in animal protein; healthy people without dietary restriction rarely experience vitamin B₁₂ deficiency. The body stores enough vitamin B₁₂ in the liver that a deficiency would take approximately 3 years to develop. Vitamin B₁₂ deficiency may be caused by poor absorption or utilization of, increased requirement for, or enhanced excretion of this vitamin. Absorption is a complex process, with about 99% of gut absorption occurring via active mechanisms (Figure 23–3). In patients with conditions that affect absorption (e.g., those with ileal diseases or who have undergone intestinal resection or gastrectomy), the reabsorption phase of the enterohepatic cycle is affected, and deficiency may result. Patients older than 50 years of age are at increased risk for vitamin B₁₂ deficiency secondary to reduced gastric acidity and the consequent decrease in release of food-bound vitamin B₁₂. Reduced intestinal motility, achlorhydria, and use of gastric acid-lowering agents in this patient population contribute to bacterial overgrowth in the small intestine, resulting in more microorganisms utilizing available vitamin B₁₂.³⁹ In addition, atrophic gastritis, a condition that affects 10%–30% of older adults, can result in macrocytic anemia owing to inadequate release of vitamin B₁₂ from foods or to inadequate production of gastric intrinsic factor (pernicious anemia). For these reasons, vitamin B₁₂ supplementation from either fortified foods or a dietary supplement is recommended for this age group, as the synthetic vitamin B₁₂ found in these formulations does not require stomach acid to ensure adequate absorption.

Figure 23–3 Vitamin B12 homeostasis. Key: CoB = Cobalamin; HC = haptocorrin; HCl = hydrochloride; IF = intrinsic factor; TC = transcobalamin.

A variety of medication classes may contribute to the development of vitamin B₁₂ deficiency, including proton pump inhibitors, histamine type 2 (H₂) receptor antagonists (H₂RAs), and metformin, among others. Development of vitamin B₁₂ deficiency has been reported after as little as 3 months of metformin therapy.^{40,41}

Vegetarians who do not consume any animal products (including infants breastfed by vegetarian mothers) also are at risk for developing vitamin B₁₂ deficiency. Vitamin B₁₂ supplementation should be encouraged for these patients.

Vitamin B₁₂ is necessary for the maintenance of myelin, and deficiency states are associated with many neurologic signs and symptoms (e.g., paresthesia, peripheral neuropathy, unsteadiness, poor muscular coordination, mental confusion, agitation, hallucinations, overt psychosis). Other manifestations of vitamin B₁₂ deficiency mimic those of folate deficiency and are manifested in organ systems with rapidly duplicating cells. Effects on the hematopoietic system result in macrocytic anemia, whereas GI effects include glossitis and epithelial changes occurring along the entire digestive tract.

Health care providers should caution patients that accurate diagnosis of a suspected anemia requires laboratory assessment of the complete blood cell profile with differential count and potentially other laboratory parameters. Anemia resulting from a folic acid deficiency should be treated with folic acid; pernicious anemia and vitamin B₁₂ deficiency should be treated with vitamin B₁₂; and iron-deficiency anemia should be treated with iron. Use of an antianemia preparation that contains multiple hematinic factors should be avoided without appropriate laboratory evaluation.

Dosing and Daily Requirements. The DRI values for vitamin B₁₂ are listed in [Table 23–4](#); a UL has not been established for vitamin B₁₂.¹⁴ Oral forms can be used if the deficiency is caused by inadequate intake. For most deficiencies caused by malabsorption, high-dose oral supplementation is appropriate because the small percentage of a high dose absorbed by passive mechanisms (not requiring intrinsic factor and binding of vitamin B₁₂ in the terminal ileum) can meet requirements; intramuscular or deep subcutaneous administration is seldom required. Vitamin B₁₂ is approved for use in the treatment of pernicious anemia and vitamin B₁₂ deficiency. Other approved uses include supplementation during periods of increased requirements (e.g., pregnancy, thyrotoxicosis, hemorrhage, malignancy, liver disease, kidney disease).¹⁹ Patients who have undergone bariatric surgery (e.g., gastric bypass, gastric sleeve resection) require lifelong vitamin B₁₂ supplementation to prevent deficiency, as do patients who have undergone resection of the terminal ileum.

Hydroxocobalamin, a prescription-only product equal in hematopoietic effect

to cyanocobalamin, may be appropriate for some patients. It is more extensively bound to proteins at the site of injection and in plasma, making renal excretion slower and prolonging the duration of action.

Safety Considerations. Excessive doses have not resulted in toxicity; however, nondeficient patients taking large quantities of the vitamin have reported no benefit.

Folic Acid (Pteroylglutamic Acid, Folate)

Function. Folate is essential for cell division, DNA production, and brain and spinal cord development. It also is used in the metabolism of various amino acids. *Folic acid* refers to the synthetic version of this vitamin found in nutritional supplements and in fortified foods; *folate* refers to the naturally occurring form found only in food sources.

Folates are present in a wide variety of food sources and are heat-labile; the folic acid content of food depends on how the food is processed. Many commercially prepared carbohydrate foods (e.g., breads, pasta) are fortified with folic acid. Folic acid, whether contained in a nutritional supplement or consumed through dietary sources, is not biologically active and must undergo in vivo enzymatic conversion to the usable form (Figure 23–4).⁴² A significant percentage of the general population may have a genetic polymorphism of methylenetetrahydrofolate reductase (MTHFR) that results in inadequate enzyme activity and inability to convert folic acid to its active form.⁴³ This genetic variance has major implications for pregnant women, because folic acid supplementation in patients with this polymorphism is not effective at reducing the risk of neural tube defects in their offspring.⁴² Other genetic defects in folate metabolism may lead to abnormalities in homocysteine metabolism (leading to elevated homocysteine levels), which have been associated with neural tube defects.⁴⁴ Folate deficiency is closely linked with deficiency of other water-soluble vitamins. Furthermore, low plasma concentrations of folate, vitamin B₆, and vitamin B₁₂ have been associated with elevated concentrations of homocysteine, which may increase the risk of cardiovascular disease. Folate supplementation may reduce elevated serum homocysteine concentrations, although this effect has not translated into improved cardiovascular outcomes.⁴¹

Figure 23–4 Folate activation pathway.

Deficiency. The requirements for folic acid are related to metabolic rate and cell turnover, and increased amounts of folic acid are needed during pregnancy, lactation, and infancy. Infection, hemolytic anemia, blood loss (in which red blood cell production must be increased to replenish blood supply), and hypermetabolic states (e.g., hyperthyroidism) also increase folic acid requirements. Because folic acid deficiency in pregnancy has been associated with an increased risk of neural tube defects in the infant, supplementation for all women of childbearing age is recommended.

Causes of folic acid deficiency include alcoholism, malabsorption, food faddism, and liver disease. Iatrogenic causes are associated with administration of certain medications, including dihydrofolate reductase inhibitors (e.g., methotrexate, trimethoprim), anticonvulsants, and sulfasalazine.¹⁹

Deficiency of folic acid results in impaired cell division and protein synthesis. Signs and symptoms of folic acid deficiency include sore mouth, diarrhea, and CNS symptoms (e.g., irritability, forgetfulness). The most common laboratory-identified feature of folic acid deficiency is megaloblastic anemia (characterized by large erythroblasts circulating in the blood).

Because vitamin B₁₂ is essential for the metabolism of folates, a megaloblastic anemia responsive to folic acid administration is a feature of vitamin B₁₂ deficiency. Folic acid given without vitamin B₁₂ to patients with inadequate intrinsic factor (pernicious anemia) or vitamin B₁₂ deficiency would correct the anemia but would not stop the damage to the CNS (characterized by lack of coordination, impaired sense of position, and various behavioral disturbances). Because folic acid can mask the signs—but not the progression—of vitamin B₁₂ deficiency, patients should receive an appropriate medical evaluation for the cause of anemia rather than an empirical vitamin supplement.

Dosing and Daily Requirements. The DRI values for folic acid are listed in [Table 23–4](#). Folic acid is approved for use in the treatment of megaloblastic anemias caused by folate deficiency. Folic acid also is approved for prevention of neural tube defects in infants of folate-deficient mothers.¹⁹

All women of childbearing age should consume synthetic folic acid at a dose of 400 mcg daily from fortified foods and/or dietary supplementation, in addition to the folate obtained from food sources.¹⁴

Persons known to have a polymorphism in MTHFR should receive a prescription vitamin containing biologically active derivatives of folic acid, available in forms such as l-methylfolate, 5-methyltetrahydrofolate calcium salt, and (6S)-5-methyltetrahydrofolate glucosamine salt.⁴²

The supplemental dose of folic acid for correction of a deficiency in adults usually is 1 mg daily, particularly if the deficiency occurs with conditions that may increase the folate requirement or suppress red blood cell formation (e.g., pregnancy, other hypermetabolic states, alcoholism, hemolytic anemia). Doses larger than the UL of 1 mg daily are rarely necessary, except in some life-threatening hematologic diseases; the Centers for Disease Control and Prevention (CDC) has recommended a 4 mg/dose of folic acid for women with a previous pregnancy affected by a neural tube defect. Maintenance therapy for deficiencies may be stopped after 1–4 months if the diet contains at least one fresh fruit or vegetable daily. For chronic malabsorption diseases, folic acid treatment may be lifelong, and parenteral doses may be required.

Safety Considerations. Folic acid toxicity is virtually nonexistent because of its water solubility and rapid excretion. Doses up to 15 mg daily have been given without toxic effect. The UL is set to minimize the risk of masking vitamin B₁₂ deficiency. Several drugs, when taken chronically, may increase the need for folic acid ([Table 23–8](#)).

Niacin (Nicotinic Acid)

The physiologically active form of niacin is niacinamide. Niacin and niacinamide are constituents of the coenzymes nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP).

Function. The niacin coenzymes are electron transfer agents; that is, they accept or donate hydrogen in the aerobic respiration of all body cells. Niacin is a unique vitamin in that humans can synthesize it from dietary tryptophan, with about 60 mg of tryptophan equivalent to 1 mg of niacin. Most people receive about 50% of their niacin requirement from tryptophan-containing proteins and the rest as preformed niacin or niacinamide.

Deficiency. The classic and only described niacin deficiency state is pellagra. Pellagra is rare, developing most often in alcoholics, poorly nourished persons of advanced age, and people on diets that severely restrict sources of niacin. It also may occur in geographic areas in which large quantities of corn are

consumed, as some of the niacin found in corn is bound to undigestible constituents, making it unavailable for absorption. Other causes of pellagra include isoniazid therapy and decreased tryptophan conversion, as in Hartnup disease and with carcinoid tumors.

Clinical features of niacin deficiency include the “three Ds” of dermatitis, diarrhea, and dementia, often accompanied by neuropathy, glossitis (manifested as a beefy red tongue), stomatitis, and proctitis. Patients exhibit a characteristic rash, with well-demarcated lesions of hard, cracked skin and blackish pigmentation that is crusty and scaly. Lesions occur primarily on sun-exposed areas, including dorsal surfaces of the hands, arms, and feet as well as the neck (Casal necklace) and face. Secondary infections may occur in such lesions. The entire GI tract is generally affected, with atrophy of its epithelium. Inflammation of the small intestine may be associated with episodes of occult bleeding and/or diarrhea.

Dosing and Daily Requirements. The DRI values for niacin are listed in [Table 23–4](#). The recommended UL for this vitamin in adults is 35 mg daily.¹⁴

Niacin requirements are increased after a severe injury, infection, or burn, or in the setting of acute illness, substantially increased caloric expenditure or decreased dietary caloric intake, or low tryptophan intake (e.g., a low-protein diet, high intake of corn as a staple in the diet). Both niacin and niacinamide are FDA-approved for the prevention and treatment of pellagra. Niacin, but not niacinamide, also is approved for adjunctive treatment of hyperlipidemia and hypercholesterolemia.¹⁹

Niacin or niacinamide, 150–500 mg daily in divided doses, is used to treat pellagra. Daily dosages of 1–2 g in 3 divided doses, up to 8 g daily, of niacin (*not* niacinamide), are used to treat hypercholesterolemia and hyperlipidemia. Niacin increases beneficial high-density lipoprotein cholesterol and decreases concentrations of potentially harmful triglycerides, total cholesterol, and low-density lipoprotein cholesterol by mechanisms unrelated to its function as an essential micronutrient. However, such high-dose niacin therapy should not be undertaken as a self-care measure; close medical supervision is required because of potentially serious associated drug-induced toxicity, primarily hepatic toxicity.

Safety Considerations. Niacinamide is associated with little toxicity; conversely, niacin toxicity can involve GI symptoms (e.g., nausea, vomiting, diarrhea),

hepatotoxicity, skin lesions, tachycardia, and hypertension. Patients should be forewarned that therapeutic doses of niacin may cause flushing and a sensation of warmth, especially around the face, neck, and ears. This reaction, which is prevalent upon initiation of therapy, may be diminished with aspirin 325 mg or ibuprofen 200 mg taken 30–60 minutes before the niacin dose, in the absence of any contraindications. Alternatively, the extended-release formulation may cause less flushing but carries a greater risk of gastric and hepatic adverse effects. Itching or tingling and headache also may occur with niacin supplementation. These effects usually will subside or decrease in intensity within 2 weeks of continued therapy. If niacin causes GI upset, it should be taken with meals; slow titration to therapeutic dosage also may reduce the risk of such adverse effects.

Because of the adverse GI effects, high doses of niacin are contraindicated in patients with gastritis or peptic ulcer disease. Niacin can provoke the release of histamine, so its use in patients with asthma should be undertaken with caution. Niacin also may impair liver function, disturb glucose tolerance, and cause hyperuricemia. Patients prescribed therapeutic doses of this nutrient must be monitored regularly for potential adverse effects.

Vitamin B₆ (Pyridoxine)

The water-soluble vitamin B₆ exists in three forms: pyridoxine (vitamin B₆), pyridoxal, and pyridoxamine. Although all three forms are equally effective in nutrition, pyridoxine hydrochloride is the form most often used in vitamin formulations.

Function. Vitamin B₆ serves as a cofactor for more than 60 enzymes, including decarboxylases, synthetases, transaminases, and hydroxylases. It is important in heme production and in the metabolism of homocysteine. As previously stated, hyperhomocysteinemia is a potential risk factor for cardiovascular disease, and it has been shown to respond particularly to folic acid supplementation but also to vitamin B₆. Whether the impact of these nutrients on homocysteine levels results in improved clinical outcomes has yet to be determined.³⁷ Limited data support a role for vitamin B₆ in the treatment of migraine headache and nausea of pregnancy; however, use of vitamin B₆ in these conditions generally is undertaken as part of an overall plan under medical supervision rather than as a sole self-care approach. Vitamin B₆ also has been suggested as a potential agent for treatment of carpal tunnel

syndrome, premenstrual syndrome (PMS), and depression; clinical research evidence supporting its use for these ailments, however, is inadequate.⁴⁵

Dietary Sources. See [Table 23–7](#). Cooking destroys some vitamin B₆.

Deficiency. Causes of vitamin B₆ deficiency include alcoholism, severe diarrhea, food faddism, malabsorptive syndromes, drugs (isoniazid and penicillamine), and genetic diseases (cystathioninuria and xanthurenic aciduria).

Manifestations of severe vitamin B₆ deficiency in infants include irritability and convulsive disorders. Medical referral of the affected child is indicated, and treatment with vitamin B₆ hydrochloride generally normalizes the electroencephalogram and resolves clinical symptoms. Symptoms and signs in adults whose diets are deficient in vitamin B₆ or who are taking a vitamin B₆ antagonist drug are difficult to distinguish from those of niacin and riboflavin deficiencies. Clinical findings may include pellagra-like dermatitis; oral lesions; peripheral neuropathy; scaliness around the nose, mouth, and eyes; and dulling of mentation. Serious deficiency signs and symptoms include convulsions, peripheral neuritis, and sideroblastic anemia, marked by inability of the bone marrow to produce normal red blood cells, with consequent iron accumulation in the mitochondria of erythroid precursors.

Dosing and Daily Requirements. DRI values for vitamin B₆ are listed in [Table 23–4](#). The FDA-approved use of this vitamin is for treatment of vitamin B₆ deficiency, including drug-induced deficiency as seen with isoniazid.¹⁹ Daily doses up to 250 mg of vitamin B₆ have been used in the treatment of hyperhomocysteinemia.³⁸ However, the UL for this vitamin is 100 mg daily for adults.¹⁴

Treatment of sideroblastic anemia requires 50–200 mg daily of pyridoxine hydrochloride to aid production of hemoglobin and erythrocytes. Several vitamin B₆–dependent inborn errors of metabolism have been shown to respond to large doses of vitamin B₆.

Safety Considerations. Vitamin B₆ may be toxic in high doses. A severe sensory neuropathy similar to that observed with the deficiency state has been reported when gram quantities were taken to relieve symptoms of PMS. Similar symptoms have been reported in women taking doses as small as 50 mg daily for PMS. Recovery occurred slowly upon withdrawal of vitamin B₆.

High daily doses of vitamin B₆ (200–600 mg) inhibit prolactin. Prenatal vitamins, which contain 1–10 mg per dosage unit, do not appear to have a significant antiprolactin effect.

Thiamine (Vitamin B₁)

Thiamine is a water-soluble, B-complex vitamin available in oral tablet and injectable dosage forms.

Function. Thiamine's active form, thiamine pyrophosphate (formerly known as cocarboxylase), plays a vital role in the oxidative decarboxylation of pyruvic acid; in the formation of acetyl coenzyme A (CoA), which enters the Krebs cycle; and in other important biochemical conversion cycles. Thiamine is necessary for myocardial function, nerve cell function, and carbohydrate metabolism. The amount of thiamine required increases with increased carbohydrate consumption.

Dietary Sources. Dietary sources highest in thiamine are listed in [Table 23–7](#). The thiamine content of food can be destroyed by heat, oxidation, and an alkaline environment, but the vitamin is stable through frozen storage.

Deficiency. The primary causes of thiamine deficiency are inadequate diet, alcoholism, malabsorptive syndromes, prolonged diarrhea, chronic furosemide therapy, increased requirements (e.g., pregnancy), and food faddism.

Thiamine deficiency in the United States is found primarily in chronic alcohol abusers. Not only is their diet often nutritionally deficient, but alcohol ingestion also impairs thiamine absorption and transport across the intestine and increases the rate of thiamine diphosphate destruction. Thiamine deficiency, also known as beriberi, may manifest with neuromuscular signs and symptoms such as peripheral neuritis, weakness, and Wernicke's encephalopathy. Cardiac dysfunction also may result, possibly accompanied by edema, tachycardia on minimal exertion, enlarged heart, and electrocardiographic abnormalities.

Dosing and Daily Requirements. The DRI values for thiamine are listed in [Table 23–4](#). Symptomatic patients are preferably treated with intravenous thiamine, owing to poor bioavailability of oral thiamine. However, long-term oral supplementation may be recommended for patients at continued risk of deficiency, including alcohol abusers and persons receiving high-dose

furosemide therapy. The FDA-approved use of thiamine is for the treatment of thiamine deficiency.¹⁹

Safety Considerations. The kidney easily clears excessive thiamine intake, and oral doses of 500 mg have been found to be nontoxic.

Potential Drug–Nutrient Interactions. Diuretics increase the urinary excretion of thiamine. Therefore, patients on chronic diuretic therapy (e.g., those with congestive heart failure or hypertension) may be at risk for subclinical thiamine deficiency and associated cardiovascular complications.

Supplementation with 100% of the DRI for this vitamin is a reasonable approach to management.⁴⁶

Pantothenic Acid, Riboflavin (Vitamin B₂), and Biotin (Vitamin H)

Other water-soluble B-complex vitamins include pantothenic acid, riboflavin, and biotin. All of these nutrients serve a variety of roles in the metabolism and conversion of carbohydrate and other macronutrients into sources of energy for numerous metabolic processes.

Functions. Pantothenic acid is a cofactor for multiple biological reactions necessary for energy synthesis. Pantothenic acid is a precursor of CoA, which is active in many biological reactions and plays a primary role in cholesterol, steroid, and fatty acid synthesis. Pantothenic acid is important for acetylation reactions and the formation of citric acid for the Krebs cycle, and it is crucial in the intraneuronal synthesis of acetylcholine. This nutrient also is important in gluconeogenesis; synthesis and degradation of fatty acids; synthesis of sterols, steroid hormones, and porphyrins; and the release of energy from carbohydrates.

Riboflavin is a water-soluble vitamin essential for cellular growth and maintenance of vision and the integrity of mucous membranes, skin, nails, and hair. Riboflavin is a constituent of two important coenzymes: flavin adenine dinucleotide and flavin mononucleotide. It has roles in numerous oxidation and reduction reactions, including the cytochrome P450 reductase enzyme system involved in drug metabolism.

Biotin is necessary for various metabolic functions, including carbohydrate, fat, and amino acid metabolism; several biotin-dependent enzymes are known to

exist.

Deficiency. Because pantothenic acid, riboflavin, and biotin are contained in many foods, deficiency states are rare and hard to detect. In malabsorption syndromes, it is difficult to distinguish manifestations of pantothenic acid deficiency from those of other nutrient deficiencies. Signs and symptoms of pantothenic acid deficiency include somnolence, fatigue, cardiovascular instability, abdominal pain, and paresthesia of hands and/or feet followed by hyperreflexia and muscular weakness in the legs. Administration of pharmacologic doses of pantothenic acid reverses these symptoms and has even been used to eliminate burning feet syndrome.

As with pantothenic acid, riboflavin deficiency, although rare, may be caused by inadequate intake, alcoholism, or malabsorptive syndromes. Deficiency of this vitamin may occur in association with other B-complex vitamin deficiency states (e.g., pellagra) or during pregnancy. Early signs of riboflavin deficiency may involve ocular symptoms, as the eyes become light-sensitive and easily fatigued. Other ocular manifestations may include development of blurred vision; itching, watering, and sore eyes; and corneal vascularization, resulting in a bloodshot appearance to the eye. Clinical findings with more advanced deficiency include stomatitis, seborrheic dermatitis, and magenta tongue.

Biotin deficiency states are rare but appear to result in signs and symptoms of nausea, vomiting, lassitude, muscle pain, anorexia, anemia, and depression. Dermatitis, a grayish color of the skin, and glossitis may be among the physical findings; hypercholesterolemia and cardiac abnormalities also may occur. Biotin deficiency in humans can be caused by ingesting a large number of raw egg whites, which contain avidin, a protein that binds biotin, thereby preventing its absorption. Persons in a rapid weight-loss program with intense caloric restriction and those with chronic malabsorption should receive supplementation, generally as part of an MVM supplement.

Dosing and Daily Requirements. AI and DRI values for these vitamins are listed in [Table 23–4](#); no UL has been established for pantothenic acid.¹⁴ The need for riboflavin appears to increase during periods of increased cell growth, such as during pregnancy and with wound healing. Absorption is enhanced when riboflavin is taken with food. The FDA-approved use of riboflavin is in the prevention and treatment of riboflavin deficiency.¹⁹ No UL has been determined for this vitamin.

Safety Considerations. Pantothenic acid, riboflavin, and biotin generally are considered nontoxic, even in large doses. The use of riboflavin typically causes a yellow-orange fluorescence or discoloration of the urine. Patients who report this effect should be reassured that this color change is normal. No known toxic concentration is associated with pantothenic acid, riboflavin, or biotin. Adverse effects have not been reported with biotin therapy; however, FDA has issued a warning regarding use of high-dose biotin supplementation, commonly found in supplements marketed for supporting hair and nail health, with certain laboratory assays yielding falsely elevated or falsely low results, depending on the test used.

Vitamin-like Compounds: Pseudovitamins

Vitamin-like compounds, or pseudovitamins, are substances that have a chemical structure very similar to that of vitamins but lack the usual physiologic or biochemical actions. That is, they are not essential for specific body functions of growth, maintenance, and reproduction. Examples of vitamin-like compounds are choline, lipoic acid, and inositol; of these substances, choline is reviewed here.

Choline

Choline is contained in most living cells and in foods. It usually is present in the form of phosphatidylcholine, commonly known as lecithin, and in several other phospholipids found in cell membranes. Intestinal mucosal cells and pancreatic secretions contain enzymes capable of splitting phospholipids to release choline. Choline also is found in sphingomyelin and is highly concentrated in nervous tissue.

Choline is available in food sources, either as choline or lecithin, and also is synthesized in the body. Therefore, choline most likely is not a vitamin. Food sources are listed in [Table 23-7](#); [Table 23-4](#) lists DRI values. An average diet furnishes ample choline daily. The recommended UL for choline is 3.5 g daily.¹⁴

Function. Choline, a precursor in the biosynthesis of acetylcholine, is an important donor of methyl groups used in the biochemical formation of other substances in vivo. Furthermore, choline and inositol are considered to be lipotropic agents (i.e., agents involved in the mobilization of lipids). Both choline and inositol have been used to treat fatty liver and abnormal fat

metabolism, but efficacy has not been established for either compound.

Deficiency. A deficiency state has not been identified in humans, possibly because choline is readily available in the diet and is synthesized in the body.

Safety Considerations. The administration of large doses of lecithin has been associated with sweating, GI distress, vomiting, and diarrhea.

Minerals

Minerals constitute about 4% of body weight, being found in a diverse array of organic compounds in the body—such as phosphorus in phosphoproteins and phospholipids, iron in hemoglobin, and iodine as a precursor for thyroxine. These elements function as constituents of many enzymes, hormones, vitamins, and inorganic compounds (e.g., sodium chloride, potassium chloride, calcium, phosphorus) that are present as free ions. Various body tissues contain differing amounts of specific minerals. For example, bone has a high content of calcium, phosphorus, and magnesium, whereas soft tissue has a high quantity of potassium. Minerals are involved in regulating cell membrane permeability, osmotic pressure, and acid–base and water balance. In addition, certain ions act as the mediators of action potential conduction and neurotransmitter action.

A well-balanced diet is required to maintain proper mineral balance. Optimal mineral intake values for humans are still imprecise; only AIs are available for trace element minerals such as chromium, fluoride, and manganese. [Table 23–5](#) lists the DRIs for select elements and minerals, and [Table 23–7](#) includes dietary sources of the minerals discussed in this chapter. Possible adverse effects of long-term ingestion of high-dose mineral supplements are often unknown, and high doses of one mineral can decrease the bioavailability of other minerals and vitamins. Pharmacists and other health care providers should be aware of select drug–nutrient interactions and mineral deficiencies that may be precipitated by certain medications ([Table 23–8](#)).

Principal Minerals in Health and Nutrition

Calcium

The most abundant cation in the body is calcium (about 1200 g).

Approximately 99% of body calcium is present in the skeleton; the remaining 1% is present in extracellular fluid, intracellular structures, and cell membranes. Calcium is a major component of bones and teeth. The calcium content in bone is continuously undergoing a process of resorption and formation. With advancing age, the resorption process comes to predominate over bone building, and a decrease in calcium absorption efficiency results in a gradual loss of bone density, leading to osteoporosis. This effect can be minimized with optimal calcium and vitamin D intake throughout the life cycle and regular participation in weight-bearing exercise; the benefit of these measures should be emphasized in patient counseling.

Function. Calcium activates a number of enzymes and is required for acetylcholine synthesis. Calcium increases cell membrane permeability, aids in vitamin B₁₂ absorption, regulates muscle contraction and relaxation, and catalyzes several steps in the activation of plasma clotting factors. Calcium also is necessary for the functional integrity of many cells, especially those of the neuromuscular and cardiovascular system.

Dietary Sources. Teenagers experiencing rapid growth and bone maturation need to consume adequate calcium, readily available in dairy products (especially milk), or as a nutritional supplement. Most adults can easily meet calcium RDAs by incorporating dairy products into the regular diet. Each 8-ounce serving of nonfat milk contains about 300 mg of calcium. As an alternative, calcium supplements usually are well tolerated in daily doses of less than 2 g. [Table 23–10](#) lists selected calcium supplements.

Table 23–10 Selected Nonprescription Calcium Supplements	
Trade Name	Primary Ingredient(s) With Amount Per Serving
Caltrate 600+D Tablets	Elemental calcium 600 mg (as carbonate); vitamin D 200–800 IU (depending on formulation)
Citracal Maximum+D3 Caplets	Elemental calcium 630 mg (as citrate); vitamin D 500 IU
Regular Strength Chewable Tablets	Elemental calcium 500 mg (as carbonate)
Viactiv Calcium plus D Soft Chews	Elemental calcium 500 mg (as carbonate); vitamin D 500 IU; vitamin K 40 mcg

The health care provider should evaluate the patient's dietary intake of calcium (including calcium-fortified foods) before recommending daily calcium supplementation. Calcium fortification is an option with various nontraditional sources (e.g., juices, breads, breakfast bars). To optimize calcium absorption, patients should avoid co-ingestion with bran, whole-grain cereals, or high-oxalate foods (e.g., cocoa, soybeans, spinach); with use of a supplement, a product co-formulated with vitamin D may be recommended if vitamin D intake from other sources is inadequate.

Deficiency. Decreased calcium concentrations may have profound and diverse consequences, including convulsions, tetany, behavioral and personality disorders, mental and growth retardation, and bone deformities (the most common being rickets in children and osteomalacia in adults). Changes that occur in osteomalacia include softening of bones, rheumatic-type pain in the bones of the legs and lower back, general weakness with difficulty walking, and spontaneous fractures. Common causes of hypocalcemia and associated skeletal disorders include malabsorptive syndromes; hypoparathyroidism; vitamin D deficiency; renal failure with impaired activation of vitamin D; long-term anticonvulsant therapy (with increased breakdown of vitamin D); and decreased dietary intake of calcium, particularly during periods of growth, pregnancy, and lactation, and among people of advanced age.

Dosing and Daily Requirements. Oral calcium supplements are approved for use in the treatment and prevention of calcium deficiency. Other FDA-approved uses include treatment of acid indigestion and hyperphosphatemia associated with end-stage renal disease.¹⁹ The recommended UL for calcium is 2–3 g daily for patients older than 1 year.¹⁵

Recommendations for calcium intake are based on elemental calcium content, not the calcium salt. Because labels can be misleading, health care providers should be familiar with the many salt forms and the different percentages of calcium in each, including carbonate (40%), citrate (21%), lactate (13%), gluconate (9%), and phosphate salts (23%–39%).⁴⁷ Calcium carbonate and calcium phosphate salts are insoluble in water and should be taken with meals to enhance absorption, which is optimal at low pH. Patients requiring supplementation who have achlorhydria or who are on chronic therapy with histamine type 2 receptor antagonists or proton pump inhibitors may benefit most from taking one of the water-soluble salt formulations (e.g.,

calcium citrate), which are absorbed more readily in basic environments.

The small intestine controls calcium absorption. Patients ingesting relatively low amounts of calcium absorb proportionately more calcium than those with adequate intake; patients taking large amounts of calcium, as in supplementation, excrete more as fecal calcium. Optimal absorption occurs with individual doses of 500 mg or less; therefore, patients taking more than 500 mg of supplemental calcium should be encouraged to take calcium in divided doses.¹⁵ In conjunction with adequate calcium and vitamin D intake, weight-bearing exercise is essential in maintaining bone mass.

Safety Considerations. Calcium in doses greater than 3 g daily can be harmful. Large amounts taken as dietary supplements or antacids can lead to accumulation of high levels of calcium in the urine with formation of renal stones, which can result in permanent renal damage. Development of hypercalcemia is possible (particularly in patients taking concomitant high-dose vitamin D preparations); this condition is associated with anorexia, nausea, vomiting, constipation, and polyuria. Increased deposition of calcium in soft tissue also can occur with hypercalcemia. The U.S. Preventive Services Task Force (USPSTF) is more conservative regarding calcium intake and recommends that daily calcium intake not exceed 1000 mg.⁴⁸ USPSTF's recommendation is based on recognition of insufficient evidence to determine whether calcium supplementation can reduce fractures in community-dwelling adults and on concerns that high-dose supplementation may increase the risk of adverse effects.

The relationship between dietary and supplemental calcium intake and potentially increased risk of cardiovascular disease has caused much controversy and uncertainty in the medical community over the past several years. A prospective study showed that supplemental calcium intake at a dose greater than 1000 mg daily was associated with an increased risk of death from heart disease in men.⁴⁹ Supplemental calcium intake at any dose in women, on the other hand, was not found to correlate with increased risk of cardiovascular disease, heart disease, or cerebrovascular event-related death in this trial. Moreover, dietary calcium intake was found to be unrelated to increased risk of cardiovascular death in either men or women, underscoring the importance of dietary calcium intake over supplemental calcium use. The study was conducted in 388,229 men and women ages 50–71 years and was designed to evaluate the effects of both dietary and supplemental calcium

intake on mortality rates for cardiovascular disease, heart disease, and stroke. Results from a post hoc analysis of the Women's Health Initiative dataset also identified no increase in risk for myocardial infarction, coronary heart disease, total heart disease, stroke, or overall cardiovascular disease in postmenopausal women receiving 1000 mg daily elemental calcium carbonate plus 400 IU daily of vitamin D₃.⁵⁰ Clearly, more information is necessary to further elucidate the correlations between calcium supplementation and cardiovascular disease risk. For patients considering calcium supplementation, a complete dietary and lifestyle evaluation is indicated to determine the possible risks and benefits of supplementation with this mineral.

Calcium intake also has been suggested to influence risk of prostate cancer. In fact, three trials have found an increased risk for prostate cancer with calcium intakes greater than 1500 mg daily from either supplements or dietary sources.⁵¹ Recommending calcium intakes closer to the DRI/RDA for men at risk for prostate cancer is reasonable until further evidence clarifies this association.

Health care providers should counsel patients about the potential for constipation associated with calcium supplementation and the importance of adequate hydration, dietary fiber, and physical activity in preventing this adverse effect.

Iron

Iron is widely available in the U.S. diet. Iron absorption from the intestinal tract is controlled by the body's need for iron, conditions in the intestinal lumen, the food source of iron, and other components of the meal (e.g., the meal's vitamin C content).

Function. Iron plays an important role in oxygen and electron transport. In the body, iron is either functional or stored ([Figure 23–5](#)).

Figure 23–5 Iron distribution in the body.

Dietary Sources. Dietary iron is available in two forms: heme and nonheme iron. Heme iron is found in meats and is reasonably well absorbed. Nonheme iron (e.g., that found in enriched grains and dark green vegetables) constitutes most of the dietary iron but is poorly absorbed. Published values of iron

content in foods are therefore misleading, because the amount absorbed depends on the nature of the iron. Although various specific ways to calculate the iron absorption from a given meal have been devised, the available iron content of foods often is estimated by assuming that about 10% of the total iron (heme plus nonheme) is absorbed if no iron deficiency is present. In the iron-deficient state, iron absorption improves to as much as 20% from an average diet. However, this estimate is not valid in the absence of heme iron. Less iron is absorbed from vegetarian diets.

Ingested nonheme iron (which is mostly in the form of ferric hydroxide) is solubilized in gastric juice to ferric chloride, then reduced to the ferrous form, and finally chelated to substances such as ascorbic acid, sugars, and amino acids. Chelates have a low molecular weight and can be solubilized and absorbed before they reach the alkaline medium of the distal small intestine, where precipitation may occur. When released at the spleen, liver, bone marrow, intestinal mucosa, and other iron storage sites, the iron is combined with apoferritin to form ferritin or hemosiderin (Figure 23–5). As needed, ferritin is released into the plasma, where it is oxidized to the ferric state and bound to a beta globulin to form transferrin. Iron is used in all cells of the body; however, most of it is incorporated into the hemoglobin of red blood cells.

Deficiency. The major mechanism of iron loss is blood loss (e.g., hemorrhagic loss, menstruation). Iron also is lost from the body with the sloughing of skin cells and GI mucosal cells, and by excretion in urine, sweat, and feces. Excess iron loss may result in iron deficiency. Early manifestations of iron deficiency are subtle, with vague symptoms. Although pallor and easy fatigability may be associated with iron deficiency, they can be attributed to other causes and are nonspecific findings. Other signs and symptoms of iron-deficiency anemia include split or “spoon-shaped” nails, sore tongue, angular stomatitis, and dyspnea on exertion. Coldness and numbness of the extremities also may be reported. Hypochromic microcytosis, as evidenced by a decreased mean corpuscular volume and low hemoglobin concentration (decreased mean corpuscular hemoglobin concentration), characterizes iron deficiency on laboratory assessment.

Iron-deficiency anemia constitutes a widespread clinical problem and is the most common form of anemia in the United States. Although it causes few deaths, it does contribute to poor health and suboptimal performance. Iron deficiency may result from inadequate intake (e.g., inadequate diet,

malabsorption) or from increased demands (e.g., pregnancy and lactation, growth, blood loss, treatment with erythropoiesis-stimulating agents). Because normal iron losses through the urine, feces, and skin are minimal, and because the major fraction of total body iron is efficiently stored and conserved (recycled), iron deficiency caused by poor diet or malabsorption develops very slowly over the course of several months.

Despite fortification of flour and public health efforts at education regarding proper nutrition, iron deficiency remains a common problem, especially during the following four life periods:

Childhood (younger than 2 years): Children may not obtain adequate iron because of the low iron content of cow's milk.

- Adolescence: In addition to blood loss with menstruation, adolescent girls are experiencing rapid physical growth, which entails an expanding red cell mass and the need for iron in myoglobin.
- Pregnancy and postpartum period: Women face the expanding blood volume of pregnancy, the demands of the fetus and placenta, and the blood loss of childbirth.
- Older adulthood: Persons of advanced age (i.e., 65 years or older) often consume inadequate dietary iron, exhibit compromised absorption secondary to achlorhydria, and experience an increased incidence of GI tract blood loss resulting from malignancy, gastric ulceration, or use of nonsteroidal anti-inflammatory drugs (NSAIDs). However, the prevalence of elevated iron stores may be significantly greater than the prevalence of iron deficiency in this age group. Therefore, in the absence of a confirmed diagnosis of iron-deficiency anemia, routine supplementation is not recommended for this age group.

Supplemental iron may be warranted for women with heavy or prolonged menstrual blood loss or for persons who frequently donate blood. Iron also may be indicated during recovery from disease- and injury-associated blood loss (e.g., with peptic ulcer disease, esophageal varices, cancer, or traumatic injury such as that incurred in motor vehicle crashes). In addition, infants being fed human milk may need supplemental iron beginning at 4–6 months of age if iron-rich foods are not introduced into the diet ([Chapter 26](#) discusses pediatric nutrition).

Chronic use of drugs such as salicylates or other NSAIDs, corticosteroids, or

anticoagulants may cause drug-induced blood loss. This effect may be the result of direct irritation of the gastric mucosa or the tendency of such drugs to cause increased bleeding. Iron supplementation should be used cautiously, if at all, in patients at high risk for GI bleeding.

Dosing and Daily Requirements. Because of the GI adverse effects associated with oral iron supplementation, the UL for elemental iron has been set at 45 mg daily for adults.¹⁴ Oral iron supplements are indicated for the prevention and treatment of iron-deficiency anemia.¹⁹

When iron supplementation is appropriate, the provider needs to evaluate which iron product is best. The choice should be based on how well the iron preparation is absorbed and tolerated and the amount of elemental iron per dose, as well as product price. Because ferrous salts are absorbed 3 times more efficiently than ferric salts, an iron product of the ferrous group usually is appropriate. Ferrous sulfate is the standard against which other iron salts are compared.

Ferrous sulfate contains 20% elemental iron, or about 65 mg in a 325 mg tablet. In patients with iron deficiency, 20% of the elemental iron (approximately 12 mg) may be absorbed. Maximum incorporation of iron into red blood cells and replacement of stores are supported with a regimen of 36–48 mg of elemental iron daily; thus, the traditional therapeutic dose for treating iron deficiency is 2–4 tablets containing 325 mg ferrous sulfate daily for 3 months. Clinical trials also have investigated the efficacy of once-daily and alternate-day dosing strategies; results suggest that these strategies may be equally efficacious or that one is better tolerated than the other in some instances. Inadequate response or worsening of symptoms during iron supplementation indicates that the patient should consult an appropriate health care provider. In cases of severe or chronic iron deficiency, when serious medical conditions have been ruled out, continuous maintenance doses of 3–4 tablets containing 325 mg ferrous sulfate daily for 3–6 months should normalize hemoglobin and replace iron stores (in the absence of ongoing losses from GI bleeding or another cause).

Table 23–11 lists comparison data on various iron salts.⁵² Ferrous salts may be given in combination with ascorbic acid to improve iron absorption. If necessary, the health care provider can encourage taking iron with fruit or juice high in ascorbic acid or with a vitamin C supplement. Combination products with iron and ascorbic acid also are available, but these products can

be expensive, and the dose of vitamin C often is inadequate to support absorption. Chemicals that may decrease iron absorption include phosphates in eggs and milk, carbonates, oxalates, tannins, and phytates in cereals.

Table 23–11 Common Nonprescription Oral Iron Formulations

Iron Formulation	Typical Dose	Percent Elemental Iron	Comparison Data
Ferrous sulfate	325 mg/ tablet	20% (65 mg/ tablet)	The gold standard for supplementation; available in multiple dosage forms; extensive history of use; proven effective; and economical.
			Delayed-release and enteric-coated products may improve tolerability, but iron absorption may be reduced.
Ferrous fumarate	60 mg/ tablet	33% (20 mg/ tablet)	No advantage over ferrous sulfate; however, may be better tolerated by some patients.
Ferrous gluconate	225 mg/ tablet	12% (27 mg/ tablet)	No advantage over ferrous sulfate; however, may be better tolerated by some patients.

Source: [Reference 52](#).

SAFETY Considerations. All iron products tend to irritate the GI mucosa and may produce nausea, abdominal pain, constipation, and (less frequently) diarrhea. These adverse effects may be minimized by reducing the dose or by giving iron with meals; however, co-ingestion of food may decrease the amount of iron absorbed by as much as 50%. The initial recommendation should be to take the iron supplement on an empty stomach; if GI adverse effects occur, the patient should be instructed to change this routine and take the iron with food.

A frequent adverse effect of iron therapy is constipation. This association has prompted the formulation of iron products that also contain a stool softener (e.g., docusate). During iron therapy, stools commonly have a black, tarry appearance because of the presence of unabsorbed iron in the feces.

Unfortunately, this finding also may indicate GI blood loss and a serious medical problem. Medical evaluation is indicated if an underlying GI condition is suspected, or if a history of GI disease exists. If the stool does not darken somewhat during iron therapy, however, the iron product may not have disintegrated properly or released the iron.

Iron must be dispensed and stored in a child-resistant container. Accidental poisonings with iron occur most often in children, who are attracted to the sugar-coated, colored tablets or who may accidentally overdose on chewable multivitamins containing iron. Such poisoning is considered a medical emergency, and any accidental ingestion of iron should be referred for evaluation by an appropriate health care provider, or to a poison control center. The clinical outcome depends on the speed and adequacy of treatment.

Symptoms and signs of acute iron poisoning include abdominal pain, vomiting, diarrhea, electrolyte imbalances, and shock. In later stages, cardiovascular collapse may occur, especially if the underlying cause has not been properly recognized and treated as a medical emergency. Treatment for iron toxicity may begin immediately at home after consultation with a poison control center or local emergency department.

Magnesium

Magnesium is essential for all living cells. It is the second most plentiful cation of intracellular fluids and the fourth most abundant cation in the body. About 2000 mEq magnesium is present in an average 70-kg adult, with about 50% of this amount in the bone, about 45% as an intracellular cation, and about 1%–5% in the extracellular fluid.

Function. Magnesium is required for normal bone structure formation and the proper function of more than 300 enzymes, including those involved with adenosine triphosphate (ATP)–dependent phosphorylation, protein synthesis, and carbohydrate metabolism. Extracellular magnesium is critical to both the maintenance of nerve and muscle electrical potentials and the transmission of impulses across neuromuscular junctions.

Magnesium tends to mimic calcium in its effects on the CNS and skeletal muscle. Magnesium deficiency blunts the normal response of the parathyroid glands to hypocalcemia. Accordingly, tetany, caused by a lack of calcium, cannot be corrected with calcium unless hypomagnesemia also is corrected.

Similarly, magnesium deficiency impairs the transport of potassium into cells; therefore, hypokalemia cannot be corrected in the presence of magnesium deficiency.

Dietary Sources. People who consume fresh foods regularly should not develop magnesium deficiency because all unprocessed foods contain magnesium (albeit in widely varying amounts). Processing (during which the germ and outer layers of cereal grains are removed) results in significant loss of available magnesium.

Deficiency. Deficiency states usually are caused by GI or renal losses. Examples of etiologic disorders and conditions are malabsorptive syndromes, acute or chronic diarrhea, steatorrhea, and drug-induced magnesium wasting in the urine, as seen with alcohol abuse, diuretic therapy, long-term use of proton pump inhibitors, calcineurin inhibitors (e.g., cyclosporine, tacrolimus), and nephrotoxins (e.g., amphotericin B). Signs and symptoms of magnesium deficiency may include neuromuscular irritability, increased CNS stimulation, delirium, and convulsions.

Dosing and Daily Requirements. Oral magnesium supplements are indicated for use in the treatment and prevention of hypomagnesemia.¹⁹ The recommended UL for magnesium is 350 mg daily for older children and adults.¹⁴

Safety Considerations. No evidence is available to suggest that oral intake of magnesium is harmful to persons with normal renal function, although diarrhea may occur with large doses. Hypermagnesemia can develop with overzealous use of magnesium sulfate (Epsom salts) or magnesium hydroxide (milk of magnesia) as a laxative, or with use of magnesium-containing antacids in patients with severe renal failure. Hypermagnesemia is associated with diminished deep tendon reflexes and variable degrees of muscle weakness, lethargy, and sedation. Progression to stupor and coma, especially at high serum concentrations, may occur. Cardiovascular manifestations may include hypotension and dysrhythmia.

Phosphorus

Phosphorus is present throughout the body, but approximately 85% of the body's store is located in bone. Phosphorus is present in nearly all foods, especially protein-rich foods and cereal grains ([Table 23–7](#)).

Function. Phosphorus is essential for many metabolic processes. It serves as an integral structural component of the bone matrix as calcium phosphate, and it is a functional component of phospholipids, carbohydrates, nucleoproteins, and high-energy nucleotides. Plasma phosphate levels are under the tight biologic control of parathyroid hormone, calcitonin, and vitamin D. DNA and RNA structures contain sugar–phosphate linkages. Cell membranes contain phospholipids, which regulate the transport of solutes into and out of the cell. Many metabolic processes depend on phosphorylation. The adenosine diphosphate (ADP)–ATP system (which provides a mechanism for the storage and release of energy for use in all of the body’s metabolic processes) involves phosphorus compounds. Additionally, an important buffer system of the body consists of inorganic phosphates.

Calcium and phosphorus have a reciprocal relationship. Both minerals are regulated partially by parathyroid hormone. Secretion of parathyroid hormone stimulates an increase in serum calcium levels through increased bone resorption, gut absorption, and reabsorption in renal tubules. Parathyroid hormone also causes a decrease in the reabsorption of phosphate by the kidney. Therefore, when serum calcium is high, serum phosphate generally is low, and vice versa.

Deficiency. Because nearly all foods contain phosphorus, deficiency states usually do not occur unless induced. For example, patients taking aluminum hydroxide as an antacid for prolonged periods may exhibit hypophosphatemia, characterized by weakness, anorexia, malaise, pain, and bone loss. Aluminum binds dietary phosphorus, forming insoluble and poorly absorbed complexes.

Dosing and Daily Requirements. The FDA-approved use for phosphorus is to alleviate signs and symptoms of deficiency.¹⁹ The recommended UL for phosphorus is 4 g daily for older children and most adults.¹⁴

Safety Considerations. GI adverse effects (e.g., diarrhea, stomach pain) have been reported with oral supplementation of phosphate salts.

Trace Elements

Trace elements, which are present in minute quantities in plant and animal tissue, are considered essential for numerous physiologic processes. Zinc and manganese are trace elements. A subset of trace elements, the “ultratrace” elements, has an estimated dietary requirement of less than 1 mg daily.

Essential ultratrace minerals include arsenic, boron, cobalt, copper, chromium, iodine, molybdenum, nickel, selenium, and silicon. Lithium and vanadium possibly are essential minerals, but further study is required to determine this status. Bromine, cadmium, fluorine, lead, and tin are not considered essential. The trace and ultratrace element content of foods typically reflects the availability of such elements in the soil in which the food was grown. One of the best defenses against deficiencies is to consume foods from a variety of geographically diverse regions.

Presented next is a review of the trace elements copper, fluoride, iodine, and zinc. These particular trace elements may need to be supplemented in patients with specialty needs. The reader is referred to more comprehensive references for detailed description of the functions, daily requirements, and safety concerns specific to other trace and ultratrace elements not included in this discussion. [Tables 23–5](#) and [23–6](#) provide a summary of DRIs and ULs for select trace elements, and [Table 23–7](#) lists food sources of these nutrients.

Copper

Copper ions exist in two states: the cuprous ion and the cupric ion (a potent oxidizing agent). Copper is similar to zinc in that it forms complexes with a number of the same chelating agents. Virtually all tissues of the body contain copper, but concentrations are highest in the liver, brain, heart, and kidney.

Function. Copper is essential for the proper structure and function of the CNS, and it plays a major role in iron metabolism. Ceruloplasmin, one of the copper metalloenzymes, is especially important in converting absorbed ferrous iron to transported ferric iron. Other copper-containing enzymes are cytochrome oxidase, dopamine beta-hydroxylase, and superoxide dismutase.

Deficiency. Copper deficiency is uncommon in humans, with a few notable exceptions. Deficiencies have been observed in premature infants; in severely malnourished infants fed milk-based, low-copper diets; after Roux-en-Y gastric bypass in persons who do not consume a supplement; and in patients receiving parenteral nutrition with inadequate copper.

One of the prominent features of copper deficiency is neurologic symptoms with gait disturbances, particularly impaired proprioception and vibration sense. Other associated clinical findings include ataxia, myelopathy, optic neuritis, polyneuropathy, and demyelination. In deficiency states, iron

absorption is impaired, typically resulting in hypochromic anemia, and spontaneous rupture of major vessels also may be observed.

Dosing and Daily Requirements. For protection against possible hepatotoxicity, the recommended UL for copper is 10 mg daily for adults.¹⁴

Safety Considerations. Wilson's disease is an inborn error of metabolism resulting in copper retention, which leads to CNS, kidney, and liver damage. Affected persons must avoid all copper supplementation. Acute symptoms and signs of copper toxicity include nausea, vomiting, diarrhea, hemolysis, convulsions, and GI bleeding. Symptoms respond to treatment with penicillamine.

Supplementation also should be avoided in patients with severe hepatic dysfunction or cholestasis, as biliary clearance of copper may be compromised.

Fluoride

Available therapeutic forms of fluoride include sodium fluoride, acidulated phosphate fluoride, and stannous fluoride. Sodium fluoride contains about 45% fluoride ion, whereas stannous fluoride contains about 24% fluoride ion.

Function. Fluoride occurs normally in bones and tooth enamel as a calcium salt. Intake of small amounts has been shown to reduce tooth decay markedly, presumably by making the enamel more resistant to the erosive action of acids produced by bacteria in the oral cavity.

Dietary Sources. Fluoride is present in soil and water, but the content varies widely from region to region. Most municipal water supplies are fluoridated to achieve 1 part per million (ppm) of fluoride, a level that has been shown to be safe and to reduce the prevalence of dental caries in children by nearly 50%. Estimates of fluoride intake from food, beverages, and water vary greatly, depending on the presence of fluoridated drinking water.

Deficiency. Fluoride deficiency states in humans, other than potential dental decay, have not been described.

Dosing and Daily Requirements. The recommended UL for this trace element is 10 mg daily for older children and adults.¹⁴

Fluoride is approved by FDA for use in the prevention of dental caries.¹⁹

Fluoride is a normal constituent of the diet in that it occurs in soils, water supplies, plants, and animals. All sources of fluoride should be evaluated before supplementation is recommended for children whose home water supply is low in fluoride. Children may obtain fluoride from other water sources (e.g., day care facility, school) or in other beverages that may contain various amounts of fluoride (e.g., soft drinks, juices, bottled water).⁵³

Sodium fluoride is available by prescription as oral tablets and solutions, topical solutions, and gels, as well as in combination products. Nonprescription topical rinses containing fluoride 0.01%–0.02% (e.g., sodium fluoride) and gels containing 0.4% stannous fluoride (e.g., Gel-Kam) are rinsed or brushed onto the teeth to reduce sensitivity and prevent dental cavities.

Safety Considerations. Excessive fluoride can be toxic. Acute toxicity should not result from the low levels present in drinking water but may occur with administration of excessive doses of fluoride supplements. Because acute toxicity affects the GI system and the CNS, it can be life-threatening. Symptoms and signs include salivation, GI distress, muscle weakness, tremors, and (rarely) seizures. Because fluoride binds calcium, symptoms of calcium deficiency (including tetany) also may be seen. Eventually, respiratory and cardiac failure may occur. All accidental ingestions of fluoride in children warrant referral for evaluation by a knowledgeable health care provider or poison control center, as fluoride intoxication may be fatal. Treatment includes precipitation of the fluoride by using gastric lavage with calcium hydroxide 0.15% solution, intravenous administration of dextrose and saline for hydration, and an appropriate calcium regimen to prevent tetany.

Chronic fluoride toxicity is manifested as changes in the structure of bones and teeth. Tooth enamel, if still under development, acquires a mottled appearance consisting of white, patchy plaques along with pitting brown stains. Prolonged ingestion of water that contains greater than 2 ppm of fluoride has resulted in a significant incidence of mottling. Extremely large doses (e.g., 20–80 mg daily) have resulted in chalky, brittle bones that tend to fracture easily, a condition known as crippling skeletal fluorosis.

Iodine

The thyroid gland contains about one third of the iodine in the body, stored in

the form of a complex glycoprotein, thyroglobulin. The only known function of thyroglobulin is to provide thyroxine and triiodothyronine, hormones that regulate the metabolic rate of cells, thereby influencing physical and mental growth, nervous and muscle tissue function, circulatory activity, and nutrient utilization.

Function. Iodine is an essential micronutrient required to synthesize thyroxine and triiodothyronine. High concentrations of iodine inhibit the release of these hormones.

Dietary Sources. The primary dietary source of iodine is iodized salt, which contains 1 part of sodium or potassium iodide per 10,000 parts (0.01%) of salt. A dose approximating 95 mcg of iodine can be obtained from about one-fourth teaspoon of salt (1.25 g). In the United States, most of the table salt products sold are iodized; however, salt used in food processing and for institutional use is not. Additional dietary sources of iodine include saltwater fish and shellfish. Produce also may be a source of iodine; the iodine content of produce reflects that of the soil in which it was grown.

Deficiency. A moderate iodine deficiency can lead to thyroid hypertrophy, resulting in goiter; severe deficiency results in hypothyroidism. The consumption of foods from diverse locations and the addition of iodide to table salt have essentially eliminated goiter as a health problem in the United States.

Dosing and Daily Requirements. Because of the fortification of salt, the iodine content of typical diets in the United States is still well above the DRI values for adults ([Table 23–4](#)). Iodine supplements are unwarranted for most people. Potassium iodide is available as a tablet, syrup, and solution, and it is included in various combination products.

Safety Considerations. Some people are allergic to iodine or organic preparations containing iodine, with development of a rash on ingestion. Symptoms of chronic iodism (iodine intoxication) may include an unpleasant taste and burning in the mouth or throat, along with sensitivity of the teeth or soreness of the gums. Other manifestations may include increased salivation, sneezing, eye irritation, and eyelid swelling. In addition, prolonged use of iodine supplementation can result in hypothyroidism.¹⁸ A UL of 1.1 mg daily in adults has been recommended.¹⁴

Zinc

Zinc is an integral component of at least 70 metalloenzymes, including carbonic anhydrase, lactate dehydrogenase, alkaline phosphatase, carboxypeptidase, aminopeptidase, and alcohol dehydrogenase.

Function. Zinc is a cofactor in the synthesis of DNA and RNA. It is involved in the mobilization of vitamin A from the liver and in the enhancement of follicle-stimulating hormone and luteinizing hormone. Zinc is essential for normal cellular immune functions, spermatogenesis, and normal testicular function. It also is important in the stabilization of membrane structure.

The divalent ion is most commonly found and used in the body. Zinc has a relatively rapid turnover rate. The balance between zinc absorption from the small intestine and excretion through feces is efficiently regulated by the body. Vegetarians may require higher amounts of zinc, because diets high in fiber and phytates hinder zinc absorption.

Dietary Sources. Most dietary zinc (about 70%) is derived from animal products ([Table 23-7](#)).

Deficiency. Zinc deficiency is not widespread in the United States. Marginally low zinc values have been associated with birth defects, growth retardation in children, and slow wound healing in adults. Additional manifestations of deficiency include immunologic abnormalities, impaired taste and smell, delayed sexual maturation, hypogonadism, hypospermia, and dermatitis.

Malabsorptive syndromes, infection, major surgery, alcoholism, pregnancy, lactation, and high-fiber diets rich in phytates predispose affected persons to zinc deficiency. Zinc depletion is relatively rare but may be seen in patients on long-term parenteral nutrition and in patients with GI tract abnormalities (e.g., fistulas or prolonged, severe diarrhea).

Zinc deficiency adversely affects DNA, RNA, carbohydrate, and protein catabolism. Iron supplements decrease zinc absorption just as zinc supplements decrease iron absorption, probably through competition for the same transport system. If both minerals are taken with a meal, the adverse interaction is less pronounced. In patients with impaired wound healing, zinc supplementation may be marginally beneficial.

Dosing and Daily Requirements. Typical Western diets supply 10–15 mg of zinc per day. Because only 10%–40% of zinc is absorbed from the GI tract, ingestion of zinc sulfate 220 mg (50 mg of elemental zinc) will supply 5–20 mg of zinc. Treatment of suspected deficiencies usually involves short-term administration of elemental zinc. Patients with large GI losses through fistulas or ostomies, or in stool with metabolic or other disorders, require larger supplemental doses of zinc. At doses above 40 mg elemental zinc per day, copper deficiency may be induced. Therefore, the UL for elemental zinc is 40 mg daily in adults if therapy with zinc is going to be long term.¹⁴ Absorption may be reduced when zinc supplements are taken with foods high in calcium or phosphorus.

Zinc has been evaluated in numerous studies as a potential agent for treatment of the common cold. However, zinc formulations and doses have varied, and trial results have been conflicting. To date, the accumulated evidence is insufficient to recommend zinc supplementation for the treatment or prevention of the common cold.⁵⁴

Safety Considerations. Zinc is most effective taken 1 hour before or 2 hours after meals, but if GI upset occurs, administration with food may minimize these effects. Zinc also is toxic; however, the emetic effect that occurs after consumption of large amounts may minimize problems with accidental overdose. Reported signs and symptoms of zinc toxicity in humans include vomiting, dehydration, poor muscle coordination, dizziness, and abdominal pain.

Nutritional Considerations in Special Patient Populations

A number of patient populations have specific dietary and supplementation counseling needs, as previously mentioned. Pediatric patients, including children and adolescents, may be at greatest risk for developing nutrient deficiency; however, these patients also may be least likely to use supplements. The pharmacist must be prepared to address concerns related to dietary insufficiency from parents and caregivers of “picky eaters” or of children with chronic diseases. Similarly, pregnancy and lactation, as conditions that represent increased metabolic demands, require the pharmacist to be prepared to educate and reinforce the importance of folic acid and other nutrients in discussions related to perinatal and preconception health throughout pregnancy and lactation. Postoperative patients who have

undergone procedures such as Roux-en-Y gastric bypass or pancreaticoduodenectomy (the Whipple procedure) may additionally require evaluation of the affected absorptive area, which may influence the recommendation to pursue maintenance supplementation of numerous nutrients. Finally, older adults, often with multiple medical conditions and taking an array of medications, may be at increased risk for nutrient deficiencies, necessitating the pharmacist's expertise in navigating appropriate selection and use of supplementation.

Multivitamin and Multimineral Supplements

Multivitamin and multimineral supplements, as previously described, are not intended to supplant a healthy, balanced diet but rather are best used to augment dietary sources and support general health. Specific nutrients of concern for inadequate intake (shortfall nutrients) recognized by the *Dietary Guidelines for Americans 2015–2020* include vitamins A, D, E, and C and folate, calcium, magnesium, and potassium, with iron also a concern in adolescent and premenopausal females. Of these nutrients, calcium, vitamin D, and potassium are of particular concern, in view of direct evidence of adverse health effects associated with inadequate daily intake and deficiency.¹³ However, MVM supplements do not target these or any other specific nutrients; rather, they provide a broad range of micronutrients. In evaluating the use of an MVM product for a particular patient, the health care provider should consider recommending a preparation that contains the basic and essential vitamins and minerals, including the following: vitamins C, B₁ (thiamine), B₂ (riboflavin), B₃ (niacin), B₆ (pyridoxine), B₉ (folic acid), B₅ (pantothenic acid), A, E, D₂ or D₃ (cholecalciferol), and K, as well as biotin, potassium, iodine, selenium, borate, zinc, calcium, magnesium, manganese, molybdenum, and beta carotene.

Owing to availability of a multitude of different nonprescription multivitamin products, further consideration of the patient's age and gender is warranted to ensure selection of a formulation that is most likely to meet individual nutritional needs. Most multivitamins formulated for women ages 18–50 years contain increased amounts of iron and folic acid to combat anemia related to menstrual blood loss and to prevent neural tube defects in the infant, respectively. Multivitamins formulated for men younger than 50 generally contain higher amounts of certain vitamins and less iron. Finally, senior multivitamins formulated for persons older than age 50 may contain more

calcium and certain B vitamins (e.g., B₆, B₁₂) but do not contain iron. Patients should be reminded to refer to the product labeling for directions for use and not to exceed the recommended intake.

For patients with questions about biochemical function, DRI values, food sources, signs and symptoms of deficiency, drug–nutrient interactions, and additional information on specific vitamins, minerals, or other dietary supplements, an excellent resource is the National Institutes of Health Office of Dietary Supplements Vitamin and Mineral Supplement Fact Sheets (with versions for both consumers and health care professionals), available at <https://ods.od.nih.gov/factsheets/list-VitaminsMinerals/>.

Assessment of Nutritional Adequacy: A Case-Based Approach

Assessing a person's nutritional status is difficult in the ambulatory environment. Clinical impressions often are erroneous, because the stages between well-nourished and poorly nourished states are not readily evident. However, guidelines may help provide a more objective assessment of nutritional status. The health care provider will need good observational skills, familiarity with questions most likely to yield helpful information (see Cases 23–1 and 23–2 for examples of questions), and knowledge of which population groups tend to be at risk for particular deficiencies. By asking key questions, the provider may detect cultural, physical, environmental, and social conditions that suggest inadequate vitamin intake. The more specific the information obtained from the patient, the more helpful the provider can be in determining the need for nutritional supplementation. Questions about the absence of different food types in the diet and about previous treatment of similar symptoms also may be important.

Although most nutritional assessment measures are beyond the scope of routine pharmacy practice, clinical observation can reveal various markers of the patient's physical status. For example, appearance of the fingernails may signal presence of malnutrition as a lack of luster to the nail surfaces and darkening at the upper ends. The texture, amount, and other characteristics of hair also may be indicators of nutritional status. The eyes (particularly the conjunctiva) may be affected in vitamin A and iron deficiencies, with ocular

manifestations including xerophthalmia, night blindness, and blurred vision. The mouth may show stomatitis, glossitis, or hypertrophic or pale gums with vitamin B deficiencies. Poor dentition may limit the foods that can be consumed by the affected person, thereby compromising intake from certain food groups such as protein. Visible goiter, poor skin color and texture, obesity or thinness relative to body habitus, and the presence of edema also may indicate malnutrition. The pharmacist should be familiar with overt but nonspecific symptoms of vitamin and mineral deficiencies for which prompt referral to an appropriate health care provider may be crucial. Additionally, it is important to recognize patients at risk for nutritional deficiency or those with increased metabolic demands (e.g., older adults, chronic alcohol abusers, pregnant and lactating women), who typically require further medical evaluation.

Checking the patient's medication history is important because of the potential for drug–micronutrient interactions ([Table 23–8](#)). Any clinical manifestations suggestive of a serious illness warrant referral to a primary care provider. Just as nutritional deficiencies may lead to disease, disease may lead to nutritional deficiencies. Patients may present with one or more deficiencies, which may be very difficult to identify. Rarely in the United States do health care providers encounter patients with severe deficiencies resulting in conditions such as scurvy, pellagra, or beriberi. Milder forms of malnutrition, however, are not uncommon.

Cases 23–1 and 23–2 provide examples of the assessment of two different patients with nutritional inadequacy.

Case 23–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history,	

including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	A patient comes to the pharmacy counter inquiring about the use of various vitamins to help prevent cancer, because a close friend was recently diagnosed with colon cancer. He indicates that he currently does not use any vitamin, mineral, or dietary supplements.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	n/a
c. Description of the patient's efforts to relieve the symptoms	n/a
d. Patient's identity	Patrick Rodriguez
e. Patient's age, gender, height, and weight	64 years, male, 5 ft 9 in., 170 lb
f. Patient's occupation	High school teacher; divorced
g. Patient's dietary habits	Eats alone most of the time: typically cereal, soymilk, and juice for breakfast; soup or sandwich for lunch; easy meals for dinner (e.g., frozen dinners with protein, starch, vegetable). Often meets a few friends to have lunch and watch sports on Saturday and/or Sunday.
h. Patient's sleep habits	n/a
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	<i>History of high blood pressure:</i> hydrochlorothiazide/lisinopril 12.5/20 mg, 1 tablet every morning
	<i>Occasional muscle aches:</i> acetaminophen 325 mg as needed
j. Allergies	Penicillin, cefazolin

k. History of other adverse reactions to medications	n/a
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	The patient's age and dietary habits may warrant consideration of a multivitamin supplement. However, no evidence to date supports the use of multivitamins to completely negate cancer risk.
3. Identify exclusions for self-treatment.	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Assess the patient's perceived need for the nutrient supplements. (2) Evaluate dietary intake from food groups, encouraging at least 5 servings of produce, 3 servings of low-fat dairy products (inquire about tolerance first; he uses soymilk for breakfast), 2 servings of protein, and 6 servings of whole-grain food sources daily. (3) Discuss which nutrients may need supplementation based on the patient's patterns of dietary intake, age, and special requirements. (4) Discuss the lack of data on and potential for harm associated with megadoses of vitamins.(5) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Regular intake of a well-balanced diet that includes fruit, vegetables, whole grains, and low-fat dairy and lean protein sources is recommended for patients with high blood pressure. A multivitamin/mineral supplement that includes vitamin B ₁₂ and a balance of other nutrients would be reasonable for Mr. Rodriguez, who prefers simple, easy meals. He also should be evaluated for adequate calcium and vitamin D intake, especially if he does not consume any dairy products.

6. Describe the recommended therapeutic approach to the patient or caregiver.	“A nutrient-rich diet has been shown to be beneficial in the prevention of many diseases, including hypertension and cancer. You can achieve this diet by (1) adding a fruit or a vegetable to your midday meal or as a snack, (2) choosing whole-grain breads and cereals, and (3) looking for healthy frozen meals and soups, as opposed to those with high levels of hidden fat and salt.”
	“A daily multivitamin/multimineral supplement would ensure you are meeting daily nutritional needs, but an ‘over 50’ product designed for people in your age group would be best. These products tend to have lower iron as well as higher amounts of vitamin B₁₂. If you are not regularly consuming dairy products, calcium and vitamin D supplementation should be considered. Check your intake of these nutrients from supplemented products, such as some orange juice brands, and discuss having your serum vitamin D concentration evaluated with your regular health care provider.”
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	“There is no evidence that vitamin supplements, in the absence of deficiency, can completely reduce cancer risk. When selecting a multivitamin, be sure to compare the level of supplementation of each nutrient, including calcium and vitamin D, with its DRI value on the product label. Additional supplementation in excess of the DRI is often unnecessary unless specifically recommended by your regular health care provider.”
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
a. Appropriate dose and frequency of administration	“Consider a daily USP-approved senior multivitamin/multimineral supplement that contains no more than 100% of DRIs for the various nutrients.”
b. Maximum number of days the therapy	n/a

should be employed	
c. Product administration procedures	"You may take your multivitamin with your current medications in the morning. However, check with your pharmacist about taking your vitamin with any newly prescribed medications."
Solicit follow-up questions from the patient or caregiver.	"What about antioxidant vitamins? Do they prevent cancer?"
Answer the patient's or caregiver's questions.	"Data from well-designed studies do not support antioxidant supplementation for the prevention or treatment of cancer. In fact, some evidence suggests potential harm from supplementation of vitamins A, E, and C, and also selenium and other nutrients, in relation to cancer risk. Therefore, dosing of these nutrients above the DRI cannot be recommended at this time."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Mr. Rodriguez in 1 week to inquire about his compliance with multivitamin recommendations and dietary modification. If necessary, reinforce the recommendations.

Key: DRI = Dietary Reference Intake; n/a = not applicable; UL = upper intake level; USP = United States Pharmacopeia.

Case 23–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and	

medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	A patient approaches the pharmacy counter seeking a recommendation for bone health support. She reports that her friend recently fell and broke her hip. She wants to start a calcium/vitamin D supplement because she has read that such supplements can reduce fracture risk.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	n/a
c. Description of the patient's efforts to relieve the symptoms	n/a
d. Patient's identity	Anna Noble
e. Patient's age, gender, height, and weight	72 years, female, 5 ft 3 in., 100 lb
f. Patient's occupation	Retired microbiologist
g. Patient's dietary habits	Tea with milk for breakfast; crackers and cheese for lunch when it is hot outside, soup if the weather is cold; easy-to-prepare microwavable meals for dinner
h. Patient's sleep habits	n/a
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	<i>High blood pressure: enalapril 2.5 mg 1 tablet daily AM</i>
	<i>Gastroesophageal reflux disease: esomeprazole 20 mg 1 tablet daily</i>

	AM
	<i>Insomnia:</i> zolpidem 5 mg as needed at bedtime
	Family history of hypertension, macular degeneration, and osteoporosis
j. Allergies	NKA
k. History of other adverse reactions to medications	None
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	According to recent warnings, use of chronic acid-suppressive medications can reduce dietary calcium uptake with potentially increased fracture risk. Furthermore, in view of Mrs. Noble's family history of osteoporosis and her small body size, she may need further medical evaluation.
3. Identify exclusions for self-treatment.	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Focus on potential drug-nutrient interactions in counseling about need for calcium supplementation. (2) Discuss the role of balanced nutrition as the ideal route of taking vitamins and minerals. Identify nutritional needs unique to this patient and micronutrients for which supplementation may be recommended. (3) Refer Mrs. Noble for medical evaluation, including serum vitamin D concentration, and osteoporosis screening. In view of her age, body habitus, family history of osteoporosis, and chronic use of acid-suppressive therapy, she may be at increased risk for osteoporosis and bone fracture. (4) Take no action.
Plan	

5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Assess the patient's perceived need for nutrient supplements. Evaluate dietary intake from food groups, encouraging at least 5 servings of produce, 3 servings of low-fat dairy products, 2 servings of protein, and 6 servings of whole-grain food sources daily.
6. Describe the recommended therapeutic approach to the patient or caregiver.	Discuss the vitamin and mineral content of the various supplements and compare the total intake with each nutrient's DRI.
	"For a woman of your age, daily intake of 1200 mg of calcium and 800 IU of vitamin D is indicated. Speak with your regular health care provider about your potential risk for osteoporosis and fracture."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Calcium and vitamin D supplementation alone may not be adequate to reduce your risk of fracture from a fall if you have underlying osteoporosis. Also, chronic use of omeprazole may further increase this risk, which complicates management. Calcium absorption from both dietary and supplement forms may be affected by stomach acid production; acid-suppressing medications such as esomeprazole may cause impaired calcium absorption. Alternative forms of calcium are available for supplementation; however, you should ask your regular health care provider whether you should continue use of acid-suppressive therapy."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	Criterion does not apply in this case.
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Mrs. Noble in 1 week to inquire about her compliance with your multivitamin recommendations and dietary modifications. If

	necessary, reinforce these recommendations. Also inquire about follow-up with her primary care provider and the need to schedule testing for serum vitamin D concentration.

Key: DRI = Dietary Reference Intake; n/a = not applicable; NKA = no known allergies.

Patient Education for Nutritional Deficiencies

The objective of self-treatment is to prevent nutritional deficiencies or to maintain present nutritional status. For most patients, carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

Vitamins, Minerals, and Trace Elements

- To ensure proper nutrition, eat a varied diet as recommended in MyPlate ([Figure 23–1](#)). Vitamin supplements are not a substitute for a well-balanced diet.
- Carefully read labels on all vitamin and mineral preparations before taking them. Note the amounts of vitamins and minerals required to meet DRI values.
- Do not take doses of vitamins and minerals higher than the recommended DRIs. High doses of vitamins or minerals may be dangerous and should not be taken indiscriminately.
- Take vitamin and mineral supplements with meals if you experience gastrointestinal symptoms.
- Women of childbearing age should take 400 mcg of supplemental folic acid in addition to maintaining a well-balanced diet. This regimen has been shown to reduce the risk of neural tube defects in the fetus.
- Be aware that iron supplements or vitamins with iron may turn the

stool black. This discoloration is not a cause for alarm, unless it is associated with other signs and symptoms consistent with a gastrointestinal bleed.

- As with any medicine, store vitamin and combination vitamin/mineral supplements out of the reach of children, especially if the product contains iron. Teach children that vitamins are drugs and potential poisons and therefore cannot be taken indiscriminately.
- Be aware that therapeutic use of niacin-containing products (but not niacinamide) may cause a flushing, itching, or tingling sensation, which should decrease in intensity with continued therapy. Taking an aspirin or other nonsteroidal anti-inflammatory drug 30–60 minutes before taking niacin may help decrease these effects.
- Do not self-medicate if you suspect a vitamin deficiency; consult an appropriate health care provider instead.

Patient Counseling for Nutrient Supplementation

The public often is exposed to exaggerated and fraudulent claims concerning vitamin products. Health care providers should keep informed about such issues in the medical and pharmaceutical literature and should not support or appear to support claims until they are substantiated by reliable clinical studies. Patients inquiring about such claims should be educated regarding potential risks with nontraditional use of vitamins.

Patients purchasing a nonprescription liquid dietary supplement should be instructed on its proper use and storage, including dilution and preparation techniques. In addition, patient counseling should include information on possible adverse effects (e.g., diarrhea, constipation).

The box “Patient Education for Nutritional Deficiencies” lists specific information to provide in patient counseling. The consumer also can be directed to websites and sources for printed literature that provide evidence-

based recommendations for vitamin and mineral supplementation, such as those listed in the “References” section for this chapter. Referral to a registered dietitian (RD) or registered dietitian nutritionist (RDN) should be considered for patients with evidence of nutritional deficiencies.

Evaluation of Patient Outcomes for Nutritional Adequacy

Nutritional therapy should involve a diet that is based on *MyPlate* and possibly the use of nutritional supplements. The health care provider should advise patients to return 30 days after implementing nutritional therapy (or sooner if symptoms worsen). Patients whose symptoms have worsened should be referred to a primary care provider. Patients who have experienced symptomatic improvement while taking nutritional supplements should nevertheless be encouraged to eat a healthful diet and not to rely on supplements as the primary source for vitamins and minerals.

Key Points for Nutritional Adequacy

- The benefits of a varied, balanced diet in terms of health maintenance and disease prevention have been demonstrated repeatedly. However, the same benefits have not been observed when suboptimal dietary intake is augmented with vitamin and mineral supplementation.
- To assess variety in food choices, the patient’s typical food pattern can be compared with *MyPlate* recommendations. Patients may be referred to an RD or RDN for personalized and more complete counseling on diet modification and nutritional supplementation.
- Overt vitamin or mineral deficiencies are rare in the United States; however, subclinical deficiencies may be contributing to chronic disease.
- The need, if any, for vitamin, mineral, or MVM supplementation should be based on the provider’s assessment of the patient’s

dietary intake, metabolic requirements, absorptive capability, and potential drug–micronutrient interactions. However, supplementation should rarely exceed 100% of the DRI. Clinical trials continue to reveal unanticipated health risks with megadoses of various micronutrients.

Chapter 24: Functional and Meal Replacement Foods

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Foods serve many purposes in our lives. Foremost is their role in survival: Foods provide us with sustenance to maintain metabolism and be physically active. Scientific research suggests that foods also affect health and wellness in specific ways, and consumers are aware of these findings. In a 2013 survey of 1005 adults selected to reflect the American population, 90% believed that health benefits other than basic nutrition are associated with certain foods.¹ Americans also report making changes to improve the healthfulness of their diet; in a 2019 survey, 23% reported actively pursuing foods or a particular diet for health benefits.² Eating more fruits and vegetables, seeking healthier protein sources, consuming more foods that contain whole grains, and maintaining a better and healthier diet overall are among the changes reported. Decisions about purchasing foods and beverages are influenced by healthfulness (62%) slightly more than convenience (57%). The perception of healthfulness depends on a number of factors, including nutrition knowledge, claims or information about health benefits of a food, attitudes and beliefs regarding health and susceptibility to disease, and trust of the information source.³ Regardless of other influences, taste (86%) continues to dominate purchasing decisions, followed by price (68%).²

Lack of time to plan and prepare meals leads health-conscious consumers to seek convenient methods to optimize nutrition for wellness and health promotion, including purchase of high-quality prepared foods and other fast yet healthy alternatives to traditional “sit-down” meals. In addition, more people who have conditions or impairments that affect their ability to obtain adequate nutrients through a regular diet are living independently, and they may seek convenient methods to supplement or replace conventional meals.

The U.S. Food and Drug Administration (FDA) is charged with regulating drugs, dietary supplements, and foods (see [Chapter 4](#)). In this context, *foods* are substances used “primarily for taste, aroma, or nutritive value.”⁴ Specific FDA regulations pertain to food safety and labeling. For all regulated foods, manufacturers are required to provide assurance in advance (premarket) that ingredients are safe, and any labeling claims must be substantiated, truthful,

and not misleading. Particular forms or uses of foods, such as infant formulas (see [Chapter 26](#)) and medical foods, are required to meet additional criteria to ensure the safety of somewhat vulnerable groups.

Although dietitians are the recognized food and nutrition experts, all health care providers should be aware of the role that foods may play in an overall plan to improve or maintain health, especially foods that have benefits beyond their basic nutrients or that help patients reach nutrient goals when healthy meals are not readily available or cannot be ingested. (See [Chapter 23](#) for discussion of vitamins, minerals and nutritional balance.) This chapter provides an overview of two main types of foods: (1) foods used for their potential health benefits—those with specific *functional* effects—and (2) foods intended as *replacements* for regular meals.

Functional Foods

A broad definition of *functional foods* (FF) is as providing “health benefits beyond those of basic nutrition.” This definition encompasses unmodified whole foods (fruits, vegetables, whole-grain products) and designer foods such as purple carrots.^{4,5} A somewhat narrower definition used by the International Life Sciences Institute restricts FF to “unmodified foods with naturally occurring bioactive components.”⁵ Examples are tomatoes, for their lycopene content, and soybeans, which provide isoflavones. The Institute of Medicine (IOM) Food and Nutrition Board restricts the definition of FF to “those foods in which the concentration of one or more ingredients has been altered to enhance the food’s contribution to a healthful diet.”^{4,5} This definition includes foods enriched or fortified with nutrients, phytochemicals, or botanical products, such as orange juice with added calcium. Elements isolated from nontraditional food sources and added to traditional foods, such as stanol esters added to margarine-type spreads, also fit this definition of FF. From this standpoint in current biomedical paradigms, plant-based foods are considered functional because of the synergy in dietary phytochemicals.^{6,7}

As defined by FDA, FF blur the distinction between drugs and foods, much as dietary supplements did until 1994, when the Dietary Supplement Health and Education Act (DSHEA) established a distinct regulatory scheme for dietary supplements.⁴ The term *functional food* is not officially sanctioned by FDA, and no legal definition or regulatory category for FF has been established. A

specific FF may be regulated as a drug or in one of several subcategories of food, depending on its intended use and labeling.^{4,5} Estimates of the global market for FF vary widely depending on the source; \$153.6 billion annually for 2019 was estimated by one source, with a projection of \$260.4 billion per year by the end of 2025.⁸ Contemporary U.S. health care reforms that mandate preventive care and emergence of the field of nutrition economics will likely fuel the growth of FF as their role in dietary recommendations and public health policy, including as a primary care option, increases.⁷

Health care providers should be familiar with FF to fully evaluate their patients' diets in relation to preventive and proactive lifestyle changes that modify risks for chronic diseases. In addition, as a trusted source of information, health care providers may influence patients' acceptance of foods with health benefits.³ Making evidence-based decisions related to the use of FF can be difficult, however, because few randomized controlled trials have been conducted, and because in many studies, only a small number of subjects are enrolled. Epidemiologic studies generally rely on recall of food intake, which obscures true associations between selected food components and disease risk. If researchers are to translate the epidemiology of dietary patterns into clinical interventions, they need a detailed look at specific diets from certain geographic regions with low and very low incidence rates for the major chronic diseases, along with detailed quantification and qualification of dietary phytochemical content.⁹ Interactions between dietary components also must be considered as contributing to beneficial effects of specific foods and dietary patterns.¹⁰ Other factors to consider include the use of biomarkers and the nutrigenomic and epigenomic effects of dietary phytochemicals in whole foods as bioactive food components in individuals.¹¹ The fact that a large number of compounds can arise from a basic chemical structure (e.g., a flavonoid) to produce distinctive effects further complicates the task of identifying active compounds within foods, because different foods within a given category (e.g., citrus) may not lead to the same outcome relative to health or disease mitigation.¹² This daunting complexity makes it challenging to design and conduct clinical trials aimed at prevention of disease. Isolating the food component and administering it as a dietary supplement rather than as an FF, in keeping with many clinical studies, would simplify study design and reduce interactions among food components. Unfortunately, available data do not support this approach, because multiple-constituent dietary phytochemicals in the matrix of plant-based whole foods appear to be safer and more effective than single and multiple-constituent high-dose dietary

supplements.^{6,10,13,14} Associations between FF or bioactive food components and health maintenance or disease prevention usually show a relative risk (RR) of <2.¹⁵ In a traditional medical toxicology model, in which exposures generally involve large doses of a single component, an RR of <2 is considered weak. By contrast, nutritional exposures are broad-based and involve small doses of multiple-component mixtures within whole foods consumed over a prolonged period. An RR of 1.5 should be ranked as “strong” for such exposures. In view of the limitations of available data and the potential for complex interactions among FF and bioactive food components, lifestyle factors, and genetics, the evaluation of FF requires examination of the totality of evidence, including that from biologic models and multiple types of research (preclinical, epidemiologic, clinical, translational).¹⁵ Dietary phytochemical patterns in whole foods and functional dietary patterns have become leading areas for FF science and functional nutrition in current research programs; these patterns will become more important in future research as understanding of these areas evolves.^{6,15} To compare findings or combine results for analysis, researchers must include preparation methods and sources of FF (whole food, isolated component, dietary supplement) in study reports.

Categories of Foods Classified as Functional Foods

FF typically fit into one of five categories on the basis of statutory definitions and regulatory guidelines for health claims on food labels:

1. Foods associated with health claims recognized by FDA
2. Foods that carry structure or function claims
3. Foods for special dietary use
4. Medical foods
5. Certain conventional foods that may be of traditional or cultural significance

A basic understanding of these categories, with recognition of those for which medical supervision is required, is essential for health care providers to optimize clinical care.

All labeling claims require FDA approval; however, the required level of

supporting scientific evidence varies depending on the category under which FF are marketed (e.g., a greater level of supporting science is required for medical foods than for structure–function claims).

Foods With Health Claims

Health claims characterize the relationship between a substance (food, food component, dietary ingredient, dietary supplement) and a disease or health-related condition.^{4,5,16} (See [Chapters 50](#) and [51](#) for discussion of dietary supplements.) Only claims about reduction of disease risk are allowed; no claim about “diagnosis, cure, mitigation, or treatment of disease” can be made. Three types of health claims can be made for conventional foods: authorized, authoritative, and qualified. Each type of claim is associated with specific levels of supportive data and specified labeling criteria. *Authorized* health claims require publication of an FDA regulation after an extensive review of the scientific literature, along with significant scientific agreement that the food/nutrient and disease relationship is well established. Of the health claims allowed for foods, authorized claims undergo the most thorough FDA review. The exact wording of the claim statement is not specified, but the statement appearing on the food label must meet specific criteria.

Statements for authorized health claims cannot quantify the degree of risk reduction, and the term *may* or *might* must be used to qualify the relationship between a food or dietary component and a disease. The label must state that the disease or health-related condition depends on many factors, implying that diet is not the only consideration in disease management. It also must indicate that the benefit related to a disease or health-related condition is part of a total dietary pattern; thus, the need for an overall healthy diet is reinforced. No health claims are permitted for foods containing more than 13 g of fat, 4 g of saturated fat, 60 mg of cholesterol, or 480 mg of sodium per reference amount customarily consumed (RACC); up to double these amounts are allowed for main dishes and meal products.^{16,17} The RACC typically is 1 serving as defined on the product label. Health claims cannot be indicated for children younger than 2 years. [Table 24–1](#) lists authorized and authoritative health claims, requirements for foods listing these health claims, and sample statements that might be used on a food label.^{4,5,16,17}

Table 24–1 Authorized and Authoritative Health Claims

Health Claim	Requirements for Foods	Sample Claim Statement(s) Containing Required Components	Selected Foods Meeting Claim Requirements
Authorized Health Claims			
Calcium–osteoporosis [Calcium and vitamin D– osteoporosis]	High in calcium [high in calcium and vitamin D] Bioavailable Phosphorus content no more than calcium content	Adequate calcium throughout life, as part of a well-balanced diet, may reduce the risk of osteoporosis. Adequate calcium and vitamin D, as part of a well-balanced diet along with physical activity, may reduce the risk of osteoporosis.	Milk Orange juice with added calcium
Sodium–hypertension	Low sodium	Diets low in sodium may reduce the risk of high blood pressure, a disease associated with many factors.	Fruits and vegetables, canned or frozen with no added salt, fresh
Dietary fat–cancer	Low fat “Extra lean” fish and game meat	Development of cancer depends on many factors. A diet low in total fat may reduce the risk of some cancers. <i>(Cannot specify types of fats or fatty acids that may be related to risk of cancer.)</i>	Fruits and vegetables, fresh, frozen, or canned Most cereals Nonfat and low-fat milk and dairy products
Dietary saturated fat and cholesterol–risk of coronary heart disease	Low saturated fat Low cholesterol Low fat “Extra lean” fish and game meat	While many factors affect heart disease, diets low in saturated fat and cholesterol may reduce the risk of this disease.	Fruits and vegetables, fresh, frozen, or canned Most cereals Nonfat and low-fat milk and dairy products
Fiber-containing grain products, fruits, and vegetables–cancer	Grain product, fruit, or vegetable containing	Low-fat diets rich in fiber-containing grain products, fruits, and vegetables may reduce the risk of some types of cancer, a	Fruits and vegetables, fresh, frozen, or canned

Health Claim	Requirements for Foods	Sample Claim Statement(s) Containing Required Components	Selected Foods Meeting Claim Requirements
	dietary fiber Low fat Good source of dietary fiber without fortification	disease associated with many factors. <i>(Cannot specify types of dietary fiber that may be related to risk of cancer.)</i>	Whole-grain breads, cereals, and pasta Brown rice
Fruits, vegetables, and grain products that contain fiber, particularly soluble fiber—risk of coronary heart disease	Fruit, vegetable, or grain product containing fiber Low saturated fat Low cholesterol Low fat Minimum of 0.6 g soluble fiber per RACC without fortification Soluble fiber content provided on the label	Diets low in saturated fat and cholesterol and rich in fruits, vegetables, and grain products that contain some types of dietary fiber, particularly soluble fiber, may reduce the risk of heart disease, a disease associated with many factors.	Fruits and vegetables, fresh, frozen, or canned Whole-grain breads, cereals, and pasta Brown rice
Fruits and vegetables— cancer	Fruit or vegetable Low fat Good source of vitamin A or C, or dietary fiber without fortification	Low-fat diets rich in fruits and vegetables (foods that are low in fat and may contain dietary fiber, vitamin A, or vitamin C) may reduce the risk of some types of cancer, a disease associated with many factors. <i>[X food is high in vitamin A, vitamin C, and/or is a good source of fiber.]</i>	Broccoli Berries Green beans Carrots Cantaloupe Citrus fruits Most dark green leafy vegetables
Folate—neural tube defects	Contains at least 40 mcg folate per serving Foods in conventional form that are a	Healthful diets with adequate folate may reduce a woman's risk of having a child with a brain or spinal cord defect.	Most dark green leafy vegetables (see Chapter 23)

Health Claim	Requirements for Foods	Sample Claim Statement(s) Containing Required Components	Selected Foods Meeting Claim Requirements
	good source without fortification Contains not more than the RDI for vitamin A as retinol, or preformed vitamin A or D Amount of folate must be in the nutrition label		
Dietary noncarcinogenic carbohydrate sweeteners– dental caries	Sugar-free Eligible substances listed in 21 CFR 101.80; examples: xylitol, sorbitol, mannitol, maltitol, isomalt, isomalulose, lactol, hydrogenated starch hydrolysates, hydrogenated glucose syrups, erythritol, D-tagatose, and sucralose Does not lower plaque pH below 5.7 when fermentable carbohydrate is present	Frequent between-meal consumption of foods high in sugars and starches promotes tooth decay. The sugar alcohols in [<i>name of food</i>] do not promote tooth decay. Short claim for small packages: Does not promote tooth decay.	Many “dietetic” sugar-free products marketed for people with diabetes Many low-calorie products marketed for weight loss

Health Claim	Requirements for Foods	Sample Claim Statement(s) Containing Required Components	Selected Foods Meeting Claim Requirements
Soluble fiber from certain foods—risk of coronary heart disease	Low saturated fat Low cholesterol Low fat Includes one or more: (1) an eligible source of whole oat or barley with ≥ 0.75 g soluble fiber per RACC, (2) Oatrim containing ≥ 0.75 g beta-glucan per RACC, (3) psyllium husk containing ≥ 1.7 g soluble fiber per RACC Amount of soluble fiber per RACC must be declared in the nutrition label	Soluble fiber from foods such as [<i>name of soluble fiber source (optional—name of food product)</i>], as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease. A serving of [<i>name of food product</i>] supplies [<i>x</i>] g of the [<i>necessary daily dietary intake for the benefit</i>] soluble fiber from [<i>name of soluble fiber source</i>] necessary per day to have this effect. <i>Note:</i> Foods with a psyllium seed husk health claim must also bear a statement on the label concerning the need to consume adequate fluids and that it should not be taken by those with difficulty swallowing.	Rolled oats, oatmeal Whole oats cold cereals Whole oat flour Oat bran Barley (whole grain, dry milled barley) Cereals with added psyllium
Soy protein—risk of coronary heart disease ^a	Contains ≥ 6.25 g soy protein per RACC Low saturated fat Low cholesterol Low fat, unless fat is from whole soybeans (no added fat)	<i>Example 1:</i> Foods containing 25 g of soy protein a day, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease. A serving of [<i>name of food</i>] supplies [<i>x</i>] g of soy protein. <i>Example 2:</i> Diets low in saturated fat and cholesterol that include 25 g of soy protein a day may reduce the risk of heart disease. One serving of [<i>name of food</i>] provides [<i>x</i>] g of soy protein.	
Plant sterol/stanol	Spreads and	<i>Example 1:</i> Foods containing at	Margarine

Health Claim	Requirements for Foods	Sample Claim Statement(s) Containing Required Components	Selected Foods Meeting Claim Requirements
esters—risk of coronary heart disease	salad dressings must contain ≥ 0.65 g plant sterol esters per RACC Spreads, salad dressings, and snack bars must contain ≥ 1.7 g plant stanol esters per RACC Low saturated fat Low cholesterol	least 0.65 g per serving of plant sterol esters, eaten twice a day with meals for a total intake of at least 1.3 g, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease. A serving of [<i>name of food</i>] supplies [x] g of vegetable oil sterol esters. <i>Example 2:</i> Diets low in saturated fat and cholesterol that include 2 servings of foods that provide a daily total of at least 3.4 g of plant vegetable oil stanol esters in two meals may reduce the risk of heart disease. A serving of [<i>name of food</i>] supplies [x] g of plant vegetable oil stanol esters. <i>Note:</i> Spreads and salad dressings with >13 g fat per 50 g of product must include a statement “See nutrition information for fat content.”	spreads with added sterol/stanol esters Orange juice with added sterol/stanol esters Nonfat milk with added sterol/stanol esters
Authoritative Health Claims ^b			
Whole-grain foods—risk of heart disease and certain cancers (Docket No. 199P-2209)	Must contain $\geq 51\%$ whole-grain ingredients by weight per RACC Low fat Must meet specified dietary fiber content: 3 g/RACC of 55 g 2.8 g/RACC of 50 g 2.5 g/RACC of 45 g 1.7 g/RACC of 35 g	Diets rich in whole-grain foods and other plant foods and low in total fat, saturated fat, and cholesterol may reduce the risk of heart disease and some types of cancer.	Low-fat whole-grain breads and cereals Whole-grain cereals and pasta Brown rice

Health Claim	Requirements for Foods	Sample Claim Statement(s) Containing Required Components	Selected Foods Meeting Claim Requirements
Whole-grain foods with moderate fat content—risk of heart disease (Docket No. 03Q-0547)	Same as above (Docket No. 199P-2209), except “low fat” is omitted	Diets rich in whole-grain foods and other plant foods and low in total fat, saturated fat, and cholesterol may help reduce the risk of heart disease.	Moderate-fat whole-grain breads and cereals
Potassium—risk of high blood pressure and stroke (Docket No. 2000Q-1582)	Good source of potassium Low sodium Low total fat Low saturated fat Low cholesterol	Diets containing foods that are a good source of potassium and that are low in sodium may reduce the risk of high blood pressure and stroke.	Many fruits and vegetables
Fluoridated water—reduced risk of dental caries (Docket No. 2006Q-0418)	Total fluoride > 0.6-1 mg/L Bottled water must meet standards of identity and quality (21 CFR 165.110) Excludes bottled water for infants	Drinking fluoridated water may reduce the risk of dental caries [or tooth decay].	Bottled water containing fluoride
Saturated fat, cholesterol, and trans fat—reduced risk of heart disease (Docket No. 2006Q-0458)	Low saturated fat Low cholesterol Quantity of trans fat on label and <0.5 g trans fat per RACC Total fat <6.5 g	Diets low in saturated fat and cholesterol, and as low as possible in trans fat, may reduce the risk of heart disease.	Fruits and vegetables, fresh, frozen, or canned Most cereals Nonfat and low-fat milk and dairy products
Substitution of saturated fat in the diet with unsaturated fatty acids—reduced risk of heart disease (Docket No.	Low fat Low cholesterol	Replacing saturated fat with similar amounts of unsaturated fats may reduce the risk of heart disease. To achieve this benefit, total daily calories should not increase.	Baked goods using polyunsaturated oils rather than butter or hydrogenated

Health Claim	Requirements for Foods	Sample Claim Statement(s) Containing Required Components	Selected Foods Meeting Claim Requirements
2007Q-0192)			oils

^a Soy protein content of foods is available from the Agricultural Research Service, U.S. Department of Agriculture (USDA). Nutrient Data Laboratory [database online]. [Search for “standard reference.”] Available at: <http://www.nal.usda.gov/fnic/foodcomp/search>. Accessed June 18, 2019. *Note:* “In the *Federal Register* of October 31, 2017, FDA published a proposed rule to revoke our regulation authorizing the use of health claims on the relationship between soy protein and coronary heart disease on the label or in the labeling of foods. We proposed this action based on our review of the totality of publicly available scientific evidence currently available and our tentative conclusion that such evidence does not support our previous determination that there is significant scientific agreement among qualified experts for a health claim regarding the relationship between soy protein and reduced risk of coronary heart disease.”¹⁶ A final statement has not been published on the proposed rule to revoke this claim.

^b Wording in the sample claim statement for authoritative claims is required by the U.S. Food and Drug Administration.

Key: CFR = Code of Federal Regulations; RACC = reference amount customarily consumed (usually 1 serving as listed on label); RDI = recommended dietary intake.

Source: References 4 and 16–19.

The manufacturer can make certain health claims for foods, food components, or dietary ingredients (but not dietary supplements) by notifying FDA after the agency receives a statement from an authoritative scientific body of the U.S. government vested with responsibility to protect public health or to conduct research related to human nutrition; this type of health claim is called an *authoritative* claim.^{4,16} The National Institutes of Health, the Centers for Disease Control and Prevention, and the National Academy of Sciences, Engineering, and Medicine are sources for authoritative claims. Significant scientific evidence supports such health claims, although FDA itself does not complete an extensive review of the data. Authoritative health claims currently recognized by FDA and required wording for the claims statement are listed in

Table 24–1.^{4,16,17}

The third type of health claim is a qualified claim. *Qualified* health claims are appropriate for use when evidence of health benefits of a food, food component, or dietary supplement is still emerging; scientific research supporting the claim tends to be limited or preliminary; and the “significant scientific agreement” level of evidence required for authorized and authoritative health claims cannot be met. **Table 24–2** lists qualified claims and specific “qualifying” terms required by FDA to indicate that evidence for the claim is limited.^{4,5,18–20} Labeling guidance issued by FDA for qualified health claims intermixes information regarding labeling of dietary supplements and conventional foods.¹⁹ **Chapter 50** provides further discussion of qualified health claims and labeling.

Table 24–2 Qualified Health Claims for Conventional Foods^a			
Food/Nutrient^b	Correlated Disease/Condition	Level of Evidence	Comments^c
Omega-3 fatty acids: EPA and DHA (Docket No. 2003Q-0401, 09/08/2004)	CHD	Supportive but not conclusive research	Total fat, saturated fat, cholesterol, and sodium maximum limits apply. Fish sources may not exceed 16 g total fat per RACC unless a statement “See nutrition information for total fat content” is included with the health claim.
EPA and DHA (Docket No. FDA-2014-Q-1146, 06/19/2019)	Blood pressure in the general population	Inconsistent and inconclusive evidence	Consuming EPA and DHA combined may reduce blood pressure and reduce the risk of hypertension, a risk factor for CHD (coronary heart disease). One serving of [<i>name of the food or dietary supplement</i>] provides [x] g of EPA and DHA.
Walnuts (Docket No. 2002P-029, 03/09/2004)	Heart disease	Supportive but not conclusive research	1.5 ounces of whole or chopped walnuts per day
Nuts (Docket No. 2002P-0505, 07/14/2003)	Heart disease	Supportive but not conclusive research	Limited to almonds, hazelnuts, peanuts, pecans, some pine nuts, pistachio nuts, walnuts; 1.5 ounces per day. Nut-containing products must contain >11 g acceptable nuts and <13 g total fat.

Food/Nutrient^b	Correlated Disease/ Condition	Level of Evidence	Comments^c
Monounsaturated fat from olive oil (Docket No. 2003Q-0559, 11/01/2004)	CHD	Limited and not conclusive evidence	Suggested intake of about 2 tablespoons (23 g) daily; replaces a similar amount of saturated fat and does not increase the total number of calories.
Unsaturated fatty acids from canola oil (Docket No. 2006Q-0091, 10/06/2006)	CHD	Limited and not conclusive evidence	Suggested intake of about 1.5 tablespoons (19 g) daily; replaces a similar amount of saturated fat and does not increase the total number of calories.
Corn oil and corn oil-containing products (Docket No. 2006P-0243, 03/26/2007)	Heart disease	Very limited and preliminary evidence	Suggested intake of about 1 tablespoon (16 g) daily; replaces a similar amount of saturated fat and does not increase the total number of calories.
Oleic acid in edible oils (Docket No. FDA-2017-Q-0807, 11/19/2018)	CHD	Supportive but not conclusive scientific evidence	Suggested intake of about 1½ tablespoons (20 g) of oils containing high levels of oleic acid; oleic acid-containing oils should replace fats and oils higher in saturated fat and not increase the total number of calories per day. One serving of [x] oil provides [x] g of oleic acid (which is [x] g of monounsaturated fatty acid).
Soybean oil (Docket No. FDA-2016-Q-0995, 07/31/2017)	CHD	Supportive but not conclusive scientific evidence	Intake of about 1½ tablespoons (20.5 g) daily of soybean oil; soybean oil should replace saturated fat and not increase the total number of calories per day. One serving of this product contains [x] g of soybean oil.
Macadamia nuts (Docket No. FDA-2015-Q-4850, 07/24/2017)	CHD	Supportive but not conclusive research	Eating 1.5 ounces daily of macadamia nuts, as part of a diet low in saturated fat and cholesterol and not resulting in increased intake of saturated fat or calories, may reduce the risk of coronary heart disease. See nutrition information for fat [and calorie] content.
100% whey protein partially hydrolyzed infant	Atopic dermatitis	Very little to little scientific	In healthy infant, not exclusively breastfed, with family history of allergy, fed the formula from birth to 4 months, claim is for reduced

Food/Nutrient^b	Correlated Disease/ Condition	Level of Evidence	Comments^c
formula (Docket No. FDA-2009-Q-0301, 05/24/2011)		evidence, uncertain	atopic dermatitis up to 3 years of age.
Ground peanuts (Docket No. FDA-2016-Q-0274, 09/07/2017)	Peanut allergy	Evidence limited to a single study	For most infants with severe eczema and/or egg allergy who are already eating solid foods, introducing foods containing ground peanuts between 4 and 10 months of age and continuing consumption may reduce the risk of developing peanut allergy by 5 years of age. Must contain the following statement in bold print: If your infant has severe eczema and/or egg allergy, check with your infant's health care provider before feeding foods containing ground peanuts.
Green tea (Docket No. 2004-Q-0427, 02/24/2011)	Cancer	May reduce risk, but very little scientific evidence	Breast cancer and prostate cancer studies were evaluated.
Tomatoes, tomato sauce (Docket No. 2004-Q-0201, 11/08/2005)	Prostate, ovarian, gastric, and pancreatic cancers	Unlikely, uncertain, or little scientific evidence	Studies are few, with major design limitations and conflicting results. Recommended amount for health benefit is ½-1 cup/week for prostate cancer, twice weekly for ovarian cancer.
Psyllium husk (Docket No. FDA-2013-Q-0167, 06/24/2014)	Diabetes	Very little scientific evidence	Claim for reduced risk of diabetesPsyllium husk must not be present in trivial amounts, although FDA does not specify a minimum amount; psyllium husk must be >95% pure to minimize potential allergenicity.
High-amylose maize starch (Docket Number FDA2015-Q-2352, 12/12/2016)	Diabetes type 2	Limited scientific evidence	The starch contains type 2-resistant starch, a type of fiber.

^a Includes only claims related to conventional foods.

^b FDA docket number is given first, followed by the date of enforcement or discretion letter.

^c Includes certain requirements for the claim.

Key: CHD = Coronary heart disease; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid.

Source: References [4](#), [5](#), [16](#), [18](#), [20](#), and [27](#).

Foods With Structure–Function Claims

Structure–function claims indicate the effect that consuming the product has on a body structure or function. These claims commonly are associated with dietary supplements but also can appear on food labels. Structure–function claims differ from health claims in that FDA validation or authorization is not required before their use; however, prior notification of FDA regarding the claim is required. In addition, structure–function claims cannot make reference regarding reduced risk of disease, because such a reference would place the product under regulation as a drug.^{4,5,16,21} For example, a probiotic yogurt marketed as for the prevention or treatment of diarrhea is considered a drug; however, if the label instead claims to “improve digestion,” this is considered an acceptable structure–function claim. Other examples of structure–function claims are statements that the product builds strong bones, supports the immune system, improves memory, maintains intestinal flora, improves strength, or promotes urinary tract health. Foods carrying a structure–function claim are considered FF; they are not considered dietary supplements when they are represented as a conventional food. For instance, margarine-type spreads with added stanol esters constitute a food, and the stanol ester is considered a food additive. However, dietary supplements in food form (drinks and bars) that are labeled and marketed as dietary supplements are regulated as dietary supplements (see [Chapter 50](#)). Distinguishing FF from dietary supplements, therefore, can be confusing.

Foods for Special Dietary Use

Foods for special dietary use, as defined by FDA, include foods used to supply particular dietary needs, or to supplement or fortify the usual diet, and marketed as such; they do not meet general dietary needs.^{4,16} Particular dietary needs may be related to the presence of physical, physiologic, pathologic, or other conditions, such as disease, convalescence, pregnancy, lactation, underweight, overweight, infancy, or the need for sodium restriction. Foods intended for use as the only nutrient source in the diet and those intended to supplement the diet by increasing total intake of a specific ingredient (vitamin, mineral, or other nutrient) also are considered to meet a particular dietary need. These foods are subject to general labeling requirements for foods, and medical supervision of their use is not required. By some definitions, foods for special dietary use are considered FF; however, this approach to marketing FF is seen in the food supply much less frequently than is structure–function labeling.

Medical Foods

Medical foods were first defined in the *Federal Register* in 1973; they were represented by an infant formula for patients with phenylketonuria, which had previously been regulated as a drug.⁴ The Orphan Drug Act Amendments of 1988 also define medical foods and require that specific criteria be met before their use and distribution. These foods are to be recommended or prescribed by a physician and used under continued medical supervision; however, they are not prescription-only products in the same manner as for prescription drugs, because they can be sold without a physician's written order. Medical foods do not occur naturally; rather, they are specially formulated and processed to meet *distinctive nutritional requirements* related to the disease or condition for which they are intended.⁴ Distinctive requirements for a select medicinal component in the food (or the food product as a whole) must be established by previous medical evaluation on the basis of recognized scientific principles. Regulations do not prohibit products from being in tablet or capsule form, and some products in these forms, especially vitamin–mineral products, marketed as medical foods may better meet the FDA definition of dietary supplements. Health care providers should be able to distinguish between true medical foods that require ongoing physician supervision and products that can be safely used for “nutritional self-care” by the public. (See

the “Medical Foods and Meal Replacement Foods” section later in the chapter for further discussion of medical foods.)

Conventional Foods

Conventional foods that do not fit into any of the preceding four categories also can be classified as FF. Research on conventional FF comes from contemporary medical ethnobiology and ethnopharmacy, with the foundation being ethnic or traditional foods associated with health benefits in various cultures and supported by epidemiologic studies. For example, long-standing systems of traditional FF use in Asia are linked epidemiologically to some of the lowest cancer rates in the world and to very low incidence of other chronic diseases.^{22,23} The strength of evidence supporting a functional role for such foods is typically weak–moderate, and clinical trials tend to be lacking; therefore, even a qualified health claim often cannot be supported at this time.⁵ However, other foods are known to contain specific compounds for which molecular functional nutrition and pharmacology studies have been conducted. Studies of dietary phytochemicals and fish oils have revealed a variety of specific phytochemicals and marine zoochemicals (e.g., epigallocatechin-3-gallate [EGCG], resveratrol, curcumin, eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA]) that modulate several molecular targets at the same time and can serve collectively as agents for chronic disease prevention and health preservation.^{14,24–26} Table 24–3 provides examples of conventional foods and the components likely responsible for their role as FF, and Table 24–4 lists examples of functional components and typical food sources.^{5,7,10–12,15,27–30}

Table 24–3 Examples of Conventional Foods Classified as Functional Foods			
Food	Functional Component(s)	Potential Health Benefit(s)	Comments
Apples	Flavonols, phenols, proanthocyanidins, soluble fiber (pectin)	Decreased risk of certain types of cancer; improved glucose and cholesterol concentrations; may contribute to maintenance of heart health	Recommend 1 apple daily, but quantity for health benefit is not defined.

Food	Functional Component(s)	Potential Health Benefit(s)	Comments
Bananas, ripe	Prebiotics, FOS	Decreased hypertension and hypercholesterolemia	Weak evidence exists for 3–10 g daily.
Berries; cherries	Anthocyanidins	Antioxidant functions; may contribute to healthy immune system	Recommend ½–1 cup daily, but amount for health benefit is not defined.
Cinnamon	Proanthocyanidins	May contribute to maintenance of urinary tract and heart health	Weak evidence exists; amount for health benefit is not well researched.
Citrus fruits	Ascorbic acid, zeaxanthin, limonene	Decreased risk of AMD ^a ; decreased cancer risk	Weak–moderate evidence exists for AMD ^a with 6 mg daily as lutein; rodent studies involved limonene and cancer.
Cocoa, chocolate	Flavonols	Antioxidant functions, decreased risk of coronary heart disease	Dark chocolate appears to be most effective.
Corn	Lutein, zeaxanthin, free stanols/sterols	Decreased risk of AMD ^a ; may decrease risk of CHD	Weak–moderate evidence exists for 6 mg daily as lutein; health claim pertains to stanol/sterol esters added to foods.
Cranberry juice ^b	Proanthocyanidins	Decreased UTI from decreased adherence of bacteria to cell walls; may also prevent adhesion of plaque-forming bacteria in the mouth	Moderate evidence exists for 300 mL daily to decrease UTI (58% reduction in bacteriuria in 150 elderly women in the first randomized controlled trial [JAMA. 1994 Mar 9; 271(10):751–4.1994]).
Cruciferous vegetables: broccoli,	Glucosinolates, indoles, isothiocyanates (sulforaphane),	Decreased risk of certain types of cancer	Weak–moderate evidence exists for >½ cup daily.

Food	Functional Component(s)	Potential Health Benefit(s)	Comments
brussels sprouts, cauliflower, cabbage	organosulfur compounds, thiols		
Dairy products, including some cheese	Conjugated linoleic acid	Decreased risk of breast cancer; possible role in improved body composition	Weak evidence exists for breast cancer link; animal studies suggest role in decreased body fat; necessary amount for health effects is not determined.
Dairy products, fermented (acidophilus milk, buttermilk, kefir, yogurt)	Probiotic organisms (lactobacilli, bifidobacteria)	Maintenance of GI tract health; decreased colon cancer risk; decreased cholesterol	See Chapter 20 for discussion of probiotics.
Eggs (yolk)	Lutein, zeaxanthin	Decreased risk of AMD ^a	Weak-moderate evidence exists for 6 mg daily as lutein.
Eggs, enriched with DHA	DHA	Decreased risk of CHD; increased HDL cholesterol	Chickens are fed fish oils or algae as a source of DHA.
Fatty fish (wild salmon, herring)	Omega-3 fatty acids	Decreased triglycerides and risk of heart disease, including fatal and nonfatal MI	Recommend 2 meals/week containing fatty fish; supportive but not conclusive evidence exists, per qualified health claim.
Flax	Phytoestrogens (lignans), alpha-linolenic acid	Decreased risk of CHD by decreasing cholesterol and platelet aggregation; weak estrogenic activity may decrease hormone-related cancers; maintenance of a healthy immune system;	Weak evidence exists for CHD association; very weak evidence exists for reduced cancer risk; amounts necessary for health benefit from flax are not defined.

Food	Functional Component(s)	Potential Health Benefit(s)	Comments
		alpha-linolenic acid may contribute to maintenance of visual function.	
Garlic	Organosulfur compounds, thiols	Decreased total and LDL cholesterol; may decrease the risk of gastric cancer; promotes healthy immune function	Weak-moderate evidence exists for approximately 1 fresh clove daily for cholesterol reduction; epidemiologic evidence for decreased cancer risk is equivocal; considerable variation exists in the amount of active compounds for available products.
Grapes, red and black	Anthocyanidins, phenolic compounds	Antioxidant functions; decreased CV risk	Epidemiologic evidence suggests inverse association with CV disease risk.
Grape juice	Resveratrol	Decreased risk of MI caused by decreased platelet aggregation	Moderate-strong evidence exists for 8-16 ounces daily.
Greens: spinach, kale, collards	Lutein, zeaxanthin	Decreased risk of AMD ^a	Weak-moderate evidence exists for 6 mg daily as lutein.
Jerusalem artichoke	Prebiotics, FOS	Decreased hypertension; decreased hypercholesterolemia	Weak evidence exists for 3-10 g daily.
Meat (beef, lamb, turkey) and milk	Conjugated linoleic acid	Antitumor effect proposed; possible role in improved body composition	Suppressed cancer cell growth in rat studies; animal studies suggest role in decreased body fat; necessary amount for health effects undetermined.
Onions,	Organosulfur compounds,	Decreased total and LDL	Weak-moderate

Food	Functional Component(s)	Potential Health Benefit(s)	Comments
leeks, scallions	thiols	cholesterol	evidence exists.
Onion powder	Prebiotics, FOS	Decreased hypertension; decreased hypercholesterolemia	Weak evidence exists for 3-10 g daily.
Rye	Phytoestrogens (lignans)	May contribute to maintenance of heart health and healthy immune system	Amounts necessary for health benefit from rye are not defined.
Tea, black	Polyphenols, flavonoids	Decreased risk of CHD	Evidence is not conclusive.
Tea, green	Catechins (epigallocatechin-3-gallate, epigallocatechin, epicatechin-3-gallate, epicatechin)	Decreased risk of certain types of cancer; improved CV health; weight control	Qualified health claim evaluation concluded green tea (not specifically catechins) is highly unlikely to reduce risk for cancer; evidence for prevention of CV disease and obesity is weak (intake estimates of >4 cups daily).
Tomatoes and processed tomato products	Lycopene	Antioxidant that efficiently decreases singlet oxygen in biologic systems; possible decreased risk of certain cancers (prostate) and MI	Evidence based on inverse associations of tissue lycopene and cancers or MI is weak; qualified health claim evaluation concluded that it is unlikely or uncertain that tomatoes or sauce (not specifically lycopene) reduces risks.
Tree nuts	Monounsaturated fatty acids, vitamin E	Decreased risk of CHD	Moderate evidence exists for 1-2 ounces daily; some nuts have qualified health claim.

^a See [Chapter 28](#) for discussion of AMD and its treatment with eye supplements.

^b In response to a health claim petition linking consumption of cranberry products to reduced risk of recurrent UTIs in healthy women, FDA issued three wording options for the qualified claim for cranberry juice beverages and for the qualified claim for the 500 mg cranberry DS. The full enforcement discretion letter that includes this information and other criteria that must be met is available at https://www.fda.gov/media/140304/download?utm_campaign=CFSANCU_CranberryQHC_07%2F21%2F2020.

Key: AMD = Age-related macular degeneration; CHD = coronary heart disease; CV = cardiovascular; DHA = docosahexaenoic acid; DS = dietary supplement; FOS = fructooligosaccharides; GI = gastrointestinal; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction; UTI = urinary tract infection.

Source: Adapted from [References 5, 7, 9–11, 15, and 27–30](#).

Table 24–4 Examples of Functional Flavonoid Components in Conventional Foods

Functional Component (Subclass of Flavonoids)	Dietary Phytochemicals	Food Sources	Potential Health Benefit(s)
Anthocyanins	Cyanidin Delphinidin Malvidin	Red, blue, and purple berries and grapes; cherries; potatoes; purple sweet potatoes; blue corn; rhubarb; plums	Augment cellular antioxidant defenses; may contribute to maintenance of brain function
Flavones	Hesperetin Naringenin	Citrus fruits and juices	Neutralize free radicals, which may damage cells; augment cellular antioxidant defenses
Flavonols	Isorhamnetin Kaempferol Myricetin Quercetin	Apples, berries, broccoli, kale, tea, onions (scallions, yellow onions; onions have highest flavonol content)	Neutralize free radicals, which may damage cells; augment cellular antioxidant defenses
Flavanols (monomers)	Catechin Epicatechin Epigallocatechin ECGEGCG	Teas (green and white), chocolate, grapes, berries, apples	May contribute to maintenance of heart health

Functional Component (Subclass of Flavonoids)	Dietary Phytochemicals	Food Sources	Potential Health Benefit(s)
Flavanols (polymers)	Proanthocyanidins Theaflavins Thearubigins	Teas (oolong and black), chocolate, apples, berries, red grapes	May contribute to maintenance of heart health and urinary tract health

Key: ECG = Epicatechin-3-gallate; EGCG = epigallocatechin-3-gallate.

Source: Adapted from [References 4, 5, and 27](#).

Protective Effects of Functional Foods

Functional Foods and Biomarkers: Epigenomics and Chemoprevention

The disposition of dietary phytochemicals is similar to that of drugs and xenobiotics to the extent that the phytochemicals can be studied with respect to their individual pharmacokinetics and pharmacodynamics.³⁰

Pharmacokinetic studies suggest that variations in disease risk or preventive efficacy of certain dietary phytochemicals may be at least partially related to genetic polymorphisms in metabolism that result in altered enzyme activity; thus, the same phytochemical may have different pharmacodynamic effects in different patients. It is unclear if genetic polymorphisms contribute to the beneficial effects associated with fiber, prebiotics, and probiotics, or whether these effects have a greater association with changes that alter the environment within the gastrointestinal (GI) tract and thereby affect the types of organisms that thrive in the GI tract. It is possible that phytochemicals, fibers, and prebiotics interact with the genetic polymorphisms or with the genetics, in general, of the probiotic organisms to induce the benefits associated with these FF components. (See [Chapter 20](#) for discussion of probiotics.) Because of such complexities, common biomarkers used to monitor a condition or health risk may be inadequate to establish a link between a phytochemical, fiber, prebiotic, or probiotic and each component's

clinical end point. IOM developed a framework for the qualification of risk biomarkers that recommends evaluation of the relationship between the clinical end point and the risk biomarker, as well as evidence that the intervention affecting the risk biomarker is concomitantly linked to the clinical end point.^{22,30} Linking biomarkers for health and disease to *epigenomics* (defined as heritable changes in gene expression that occur without a change in DNA sequence)²⁶ is a major challenge in FF research.¹¹

Fiber

Fiber is a component of FF that has been widely studied for associations with potential health benefits. *Fiber* consists of dietary components that humans cannot digest, including plant cell walls; nonstarch polysaccharides from seaweed, microorganisms, or seed husks (psyllium); resistant starches; and nondigestible oligosaccharides.³¹ The terms *dietary fiber* and *functional fiber* are related to dietary reference intakes (see [Chapter 23](#)) and distinguish between sources of fiber.^{31,32} However, because of the heterogeneous composition of these substances, dietary fiber has no chemical definition, and until 2016, FDA regulations had no established definition for its use.³³ Based on the IOM definition, *total fiber* is the sum of dietary and functional fiber.³¹ In its amendment to food labeling regulations, FDA determined that “total fiber” should be used on food labels, rather than listing dietary fiber and functional fiber separately. *Dietary fiber* is defined by IOM as “nondigestible carbohydrates and lignin that are naturally occurring (intrinsic and intact) in plants”; FDA added “and insoluble carbohydrates (with 3 or more monomeric units)” to its definition.^{31,33} Per the IOM definition, *functional fiber* is “isolated nondigestible carbohydrates that have beneficial physiologic effects in humans, including fiber extracted or modified from plants or animal sources”; FDA also included “synthetic non-digestible carbohydrates (with 3 or more monomeric units)” in the regulation. Through a rigorous science review, FDA identified isolated or synthetic nondigestible carbohydrates that were determined to have health benefits and to meet the agency’s new definition of fiber, provided a document with data used to determine fibers that did not meet the new definition, and published guidance regarding information that should be submitted for a scientific evaluation to prove that other purified or isolated fibers meet the agency’s definition of fiber.^{34–36}

FDA evaluated the literature for 26 fiber types that were determined to not meet the agency’s definition of fiber.³⁵ The final report included background

information and various physiologic effects reported for the fibers, such as effects on blood cholesterol, blood glucose, laxation or bowel function, and mineral absorption. Only 7 of these fibers were deemed to meet FDA requirements for fiber and were listed in the Code of Federal Regulations.³⁴ Two of the fibers, beta-glucan soluble fiber and psyllium husk, already had in place authorized health claims related to the risk of coronary heart disease.^{16,34} A general authorized health claim exists for fruits, vegetables, and grain products that contain fiber, particularly soluble fiber, for reducing risk of coronary heart disease. The other recognized fibers included cellulose, guar gum, pectin, locust bean gum, and hydroxypropylmethylcellulose. A general authorized health claim also has been presented for benefit of fiber-containing grain products, fruits, and vegetables in reducing cancer risk.¹⁶ Numerous products currently considered fiber by many manufacturers were not included in the FDA rule, leading to submission of a large number of comments (i.e., informed complaints) to the agency and a suggestion that the current guidance on fiber requires major revision.³⁷ At this time, however, more rigorous research will be required to have such “fibers” added to the list of FDA-recognized fibers. Research should include the effects of extracting fiber from cell walls, because the effects of such extracted fiber may differ from those of in situ fiber owing to altered chemical and physical properties. Viscosity and fermentability were not included in FDA’s definition for fiber, although these factors may have important correlates with health effects.^{38,39} The terms *soluble fiber* and *insoluble fiber*, as used in this discussion, remain pervasive in both professional and nonprofessional literature. FDA regulations require listing the number of grams of dietary fiber (denoting soluble or insoluble fiber is voluntary) on the nutrition label if a claim for fiber is included on the product.³⁴

Recommended and Actual Intake

As published by IOM, adequate intakes (AIs) for total fiber are in the range of 21–38 g daily, with amounts for women and older people being lower than those for men and younger people.³² (See [Chapter 23](#) for general information on AIs.) Values for AIs are based on usual caloric intake in each age group and a baseline of 14 g of dietary fiber per 1000 calories, which appears to be the amount needed to promote heart health.^{31,40} Unfortunately, actual mean fiber intake is only about 15–17 g daily for women and 17–20 g daily for men; progress toward meeting the goals has been minimal over the past 2 decades.^{41,42}

Soluble and Insoluble Fibers

Soluble fibers typically undergo substantial degradation and fermentation in the colon; negligible degradation and fermentation occur with most insoluble fibers. [Table 24–5](#) outlines food components, food sources, and functional fiber sources typically associated with soluble and insoluble fibers. The food sources listed are good to excellent sources of fiber based on tests previously accepted for identifying fiber content⁴²; however, not all fibers listed in the table are recognized in the newer FDA regulations for nutrient labeling.¹⁷

Table 24–5 Components and Sources of Soluble and Insoluble Fiber ^a		
Component	Sources	
	Soluble Fiber	Insoluble Fiber
Food component	Pectins, gums, mucilages, algal substances, some hemicellulose	Cellulose, lignin, most hemicellulose
Food sources with ≥2.5 g of total fiber per serving ^b	Cereals: oat bran (uncooked, ²/₃ cup), oatmeal (cooked, 1 cup) Fruits: apples and pears with skin on, oranges (1 medium), figs and prunes (3 small) Vegetables: broccoli, carrots, cauliflower, corn, kale and other greens, dark green or loose leaf lettuce, peas, squash, zucchini (cooked, ³/₄–1 cup)	Bran and whole-grain (corn, rye, wheat) products: bran cereals (dry cereal, ¹/₃–1 cup), brown rice (cooked, 1 cup), whole wheat bread (2 slices) Dried beans: lima, kidney, pinto, white (cooked, ¹/₄–¹/₂ cup)Dried peas: green, split (cooked, ¹/₄–¹/₂ cup)
Functional fiber sources	Beet fiber, FOS, guar gum (galactomannan, Benefiber), inulin, karaya gum, konjac mannan (glucomannan), locust bean gum, pectin, psyllium (ispaghula seed husk)	Calcium polycarbophil, methylcellulose, powdered cellulose, soy polysaccharide (also has significant soluble fiber effects)

^a Not all fibers listed in the table are recognized by the U.S. Food and Drug Administration in regulations for nutrient labeling.

^b Serving size shown in parentheses. The food sources listed are good (2.5–4.9 g of fiber per serving) to excellent (5 g or more of fiber per serving) sources of total dietary fiber and are listed under the fiber type that exemplifies their predominant health effects.

Key: FOS = Fructooligosaccharides.

Source: Adapted from [References 31, 34, and 42](#).

Methods of Increasing Fiber Intake

Table 24–6 lists suggestions for increasing fiber content in the diet. Caution is advised with the use of fiber-containing products in patients with poor GI motility or underlying GI dysfunction, including narcotic-associated dysmotility. Inadequate fluid intake also may contribute to GI distress from a high-fiber diet. It is advisable to gradually increase fiber, because a sudden increase can cause bloating, gas, and, occasionally, diarrhea. A reasonable approach is to add 1–2 servings of foods that are abundant in fiber (**Table 24–5**) to the diet every few days until the goal for fiber intake is reached. Reading ingredient labels is essential to evaluate adequacy of fiber content, especially for breads and cereals, in which a *whole* grain should be the first ingredient listed.

Table 24–6 Methods for Increasing Fiber in the Diet

- Eat breads containing “wheat berries,” whole wheat flour, or other whole grains as the first ingredient on the label. These products should replace breads from refined flours that do not include whole grains.
- Replace part of refined (non-whole-grain) cereals with whole-grain cereal for persons who prefer refined cereals; or mix very-high-fiber cereals into a favorite brand of cereal.
- Eat oatmeal as a hot breakfast cereal, or select a cold cereal with oats or whole grain as the primary ingredient.
- Sprinkle bran on cereal, yogurt, or other foods.
- Eat brown rice, whole wheat pasta, and whole-grain crackers rather than white rice and products from refined grains.
- Add fruit to breakfast cereals, breads, yogurt, and salads.
- Select recipes that use whole-grain flours, and/or add rolled oats to baked goods.
- Select recipes for baked goods that include apples, applesauce, carrots, pumpkin, or other fruits or vegetables as a significant ingredient.
- Add kidney, garbanzo, navy, or other beans to salads and soups, including canned soups. Rinse and drain canned beans to reduce components prone to cause intestinal gas.
- Serve fruit and/or vegetable salads with picnic lunches instead of potato chips.
- Serve canned beans (black, kidney, white, baked) as an alternative protein source.
- Eat fresh or dried fruit for snacks and desserts; frozen and canned fruits (in juice) also can be used.

- Use a low-fat refried bean dip or hummus with whole wheat baked tortilla chips for snacks.
- Eat fruits and vegetables, including potatoes, with the skin on.
- Select snack or meal replacement bars containing at least 2.5 g of fiber per serving.
- Include “finger food” vegetables (carrots, celery, cauliflower pieces, broccoli florets) in lunch boxes and as snacks.
- For children, make animal or other fun shapes from vegetable pieces.
- Eat nuts and/or seeds for snacks, or add to mixed dishes, salads, breads, and cereals.

Benefits of Fiber

The generally accepted benefits of fiber are laxation effects, normalization of blood lipid concentrations, and attenuation of blood glucose response.^{5,36,38,42} These benefits are the accepted measures of efficacy that are required for label claims of fiber content in Canada and the United States.^{32,33} Other benefits of fiber, such as weight control, have been suggested in humans; however, results of relevant studies are limited and conflicting.

Laxation

Stool characteristics associated with *laxation*, or improved bowel function, include increased stool bulk, weight, and water content; decreased stool transit time and normalization of stool frequency to once daily; reduced symptoms of constipation; and an overall improvement in ease of defecation. Epidemiologic studies strongly support the positive role of fiber from whole grains, fruits, and vegetables in laxation. Insoluble fiber has been associated most frequently with improved laxation, although evidence also indicates some soluble fibers have similar effects. The role of functional fibers in laxation is well accepted, and adequate scientific evidence exists to support FDA approval of some fibers as nonprescription bulking agents for treatment of *occasional* constipation, as discussed in [Chapter 15](#). Studies supporting the efficacy of bulk-forming fibers in *chronic* constipation tend to be of intermediate to low quality, and results are mixed.

Normalization of Blood Lipid Concentrations

Data on reduced risk of coronary heart disease (CHD) with intake of certain fibers are sufficient to support an FDA-authorized health claim ([Table 24–1](#)).^{4,5,16} Multiple epidemiologic studies have reported a reduced risk of CHD or cardiovascular disease (CVD) with high dietary fiber intake and/or fiber-rich

foods. The relationship appears to hold over many years and across ethnic groups. **Table 24–7** summarizes data related to risk of CHD from several large, well-designed prospective epidemiologic studies with longer-term follow-up and pooled data studies.^{40,43–49}

Table 24–7 Summary of Selected Studies Related to Fiber and Risk of Coronary Heart Disease (CHD) and Improved Glucose Control

Study Name and Population Characteristics^a	Follow-up Time (Years)	Results/Conclusions
Pooled data, cohort studies; total of 672,408 men and women in 18 studies ⁴³ ; ages 25–99 years		<i>CHD</i> : RR 0.93 (7% decrease) for all CHD events and 0.83 (17% decrease) for CHD (CHD-related) mortality; RR 0.92 for all CHD events and RR 0.76 for CHD mortality for each 10 g daily increment of total dietary fiber. Inverse relationship between intake of dietary fiber from cereal sources and fruits and risk of CHD; intake of dietary fiber from cereal sources only and CHD mortality; soluble and insoluble fiber intake and risk of CHD/CHD mortality.
Nurses' Health and Health Professionals Follow-up Studies ⁴⁴ ; prospective cohort design; 2258 women and 1840 men; ages 30–75 years	22–32	<i>CVD</i> : HR 0.75 for all-cause mortality after MI for highest fifth quintile fiber intake; stronger association for cereal fiber, with HR 0.73 for all-cause mortality and HR 0.72 for CVD mortality; with increased fiber intake from before to after MI, HR 0.69 for all-cause mortality
Pooled data, cohort studies ⁴⁵ ; total of 2,254,632 men and women in 22 studies; ages 16–79 years	6–22	<i>CVD/CHD</i> : RR 0.91 (9% decrease) for CVD and CHD for each 7 g daily increment of total dietary fiber; inverse relationship between intake of insoluble fiber and fiber from cereal and vegetable sources and risk of CHD/CVD; inverse relationship between fruit fiber intake and risk of CVD
Pooled data, prospective cohort studies ⁴⁶ ; total of 3,600,126 men and women in 15 studies; ages 20–85 years	5.9–40	<i>CVD/CHD</i> : RR 0.77 for CVD mortality and 0.76 for CHD mortality; RR 0.91 for CVD mortality and RR 0.89 for CHD mortality for each 10 g daily increment of total dietary fiber

Study Name and Population Characteristics ^a	Follow-up Time (Years)	Results/Conclusions
		High intake of dietary fiber of 29.6 g daily reduced CVD mortality by 23%, and 23.2 g daily reduced CHD mortality by 24%, compared with low intake of 14 g daily and 12.5 g daily.
PREDIMED Study ⁴⁷ : observational cohort design; 7216 men and women; ages 55–75 years	5.9	CVD: HR 0.59 (41% lower risk) in highest quintile of fiber intake of median 35 g daily, compared with lowest quintile of median 17 g daily; inverse relationship between baseline fiber intake and fruit consumption and CVD-related mortality
		Subjects who increased their fruit consumption to >210 g daily had 41% lower all-cause mortality. Participants were free of CVD at baseline.
Cardiovascular Health Study, fiber intake analysis ⁴⁰ : cohort design; 3588 men and women; ages ≥65 years (average 72 at baseline)	8.6	CHD/CVD: Cereal fiber intake was inversely associated with incident CVD. HR 0.79 (21% lower risk) in highest quintile of fiber intake versus lowest quintile. The difference was seen with about 4.6 g fiber daily (2 slices whole-grain bread). Lower risk predominantly seen with fiber in dark bread (whole-wheat, rye, pumpernickel). Fruit and vegetable fiber intake was not associated with incident CVD. Participants were free of known CVD at baseline.
NIH-AARP Diet and Health Study ⁴⁸ : 367,442 men and women; ages 50–71 years	14 (5,148,760 person-years ^b)	CVD/Glucose: Fiber intake from whole grains was inversely associated with all-cause mortality and risk of death from CVD and diabetes. All-cause mortality was decreased by 17% in the highest quintile for whole grains, 1.2 oz eq daily, and 19% for highest quintile for cereal fiber, 10.22 g daily.
Pooled data, prospective cohort studies ⁴⁰ : total of 91,058 men and 245,186 women in 10 studies; ages 35–98 years	6–10	CHD: RR for all coronary events 0.86 (14% decrease) and RR 0.73 (27% decrease) for coronary death for each 10 g daily increment of total dietary fiber. For cereal fiber, RR 0.9 for all coronary events and RR 0.75 for death; for fruit fiber, RR 0.84 and 0.7; for vegetable fiber, RR 1.00 for all coronary events and death. Results were similar for men and women.
Pooled data, prospective cohort studies ⁴⁹ : 488,293 men and	10.8	Glucose: RR 0.81 (19% decrease) for type 2 DM with total dietary fiber intake. For cereal fiber, RR 0.77; for fruit fiber, RR 0.94; for insoluble fiber, RR 0.75. 34% lower risk of DM with high fiber intake of 35 g daily compared with that for the lowest quintile of

Study Name and Population Characteristics^a	Follow-up Time (Years)	Results/Conclusions
women in 17 studies		15 g daily. RR 0.94 (6% decrease) for DM per 2 g daily increment in cereal fiber intake.
Nurses' Health Studies: NHS-I and NHS-II ⁴⁰ : cohort design; total 161,737 women; NHS-I: 73,327, ages 37–64 years; NHS-II: 88,410, ages 26–46 years	12–18	<i>Glucose:</i> For each 40 g increment in whole-grain intake, multivariate analysis indicated RR for DM of 0.54 (NHS-I) and 0.64 (NHS-II). BMI accounted for 42% and 57% of the association with RR after adjustment for BMI of 0.7 and 0.83, respectively, for NHS-I and NHS-II.

^a Number of participants included in the analysis is not always the entire study population; meta-analyses may include subsets of data from more than one trial.

^b One person-year is equivalent to data for one person followed for 1 year.

Key: BMI = Body mass index; CVD = cardiovascular disease; DM = diabetes mellitus; HR = hazard ratio; MI = myocardial infarction; RR = relative risk.

Source: [References 40](#) and [43–49](#).

The key to fiber's ability to lower cholesterol and reduce CHD risk appears to be consuming an adequate quantity of highly viscous fiber, primarily from whole-grain cereal (oats, barley, rye) and beans (legumes), or from guar gum, pectin, and psyllium. More recent data suggest that fruit fiber may have a beneficial effect relative to CHD/CVD, whereas the association with vegetable fiber is less clear.

Attenuation of Blood Glucose Response

Multiple large, well-designed prospective epidemiologic and cohort studies with longer-term follow-up have reported an association between consumption of fiber and attenuation of blood glucose response, improved

insulin response, and/or reduced risk of diabetes, as summarized in [Table 24–7](#) studies.^{40,43–49} The overall conclusion from these studies is that an inverse relationship exists between risk of diabetes and intake of dietary fiber. Intake of cereal fiber appears to be most frequently related to improved glucose control and/or reduced risk of diabetes; foods most likely to provide a positive effect include cereal grains such as oats, barley, and rye. Some legumes (beans), fruits, and vegetables, as well as guar gum and pectin, also may have a beneficial effect on glucose control. Available evidence suggests that nonviscous fibers, such as wheat bran, have little effect on glycemic control.

Weight Loss and Maintenance

Epidemiologic studies show a lower body mass in subjects who eat a high-fiber diet and greater incidence of obesity in those with low intake of dietary fiber.^{31,40} Interventional studies show mixed results with high-fiber diets and weight loss, although less weight gain over time is associated with higher intake of whole grains.⁵⁰ Research suggests that fiber intake may influence body weight through various mechanisms, such as delayed gastric emptying, prolonged small bowel transit time and subsequent effects on peptides associated with satiety and gut function, activation of the “ileal brake” feedback mechanism, and stimulation of colonic cells, resulting in production of appetite-regulating hormones.⁵¹

Assessment of Functional Food Use: A Case-Based Approach

FF play a role in preventing disease and optimizing health. For patients who have mild signs of or are at risk for CHD, these foods may be a viable alternative to pharmacotherapy, as Case 24–1 illustrates.

Case 24–1

Relevant Evaluation	Scenario/Model Outcome

Criteria	
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient has no symptoms but recently had a health assessment at work and was told that she is at risk for coronary heart disease because of her family history. She says she does not feel sick, but she does not want to end up taking a "bunch of pills every day" like her mother and oldest brother. She wants to do what she can to avoid heart disease and is particularly interested in "functional foods" because of a healthy lifestyle program she recently watched.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	n/a
c. Description of the patient's efforts to relieve the symptoms	n/a
d. Patient's identity	Angela Barcelona
e. Patient's age, gender, height, and weight	30 years, female, 5 ft 4 in., 190 lb
f. Patient's occupation	Third-grade teacher

g. Patient's dietary habits	Eats breakfast most mornings: typically a cup of tea and cereal bar from home or a fast food English muffin with egg and sausage.
	Lunch: usually has a sandwich with potato chips and soft drink from the cafeteria.
	Afternoon snack: typically has a candy bar or granola bar.
	Dinner: Usually has meat (beef, pork, or chicken mostly) and fish "every once in a while when someone has gone fishing"; rice or pasta most nights; fresh, frozen, or canned vegetable 4-5 times per week; sweet dessert (cake, pie, baked goods) or ice cream 5-6 times a week; typically has a soft drink with dinner and occasionally an alcoholic drink.
h. Patient's sleep habits	Usually sleeps about 8 hours per night.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	No medical conditions. She takes a birth control pill and multivitamin with folate daily.
j. Allergies	NKDA
k. History of other adverse reactions to medications	None
l. Other (describe) -----	n/a
Assess	
2. Differentiate patient's signs/symptoms and correctly identify the patient's	Mrs. Barcelona has no signs or symptoms of disease but wants to follow a preventive strategy of a healthy diet.

primary problem(s).	
3. Identify exclusions for self-treatment.	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer Mrs. Barcelona to her regular health care provider for a more thorough assessment for heart disease and evaluation of her risk. (2) Refer Mrs. Barcelona to a registered dietitian for comprehensive nutritional assessment and counseling. (3) Inform Mrs. Barcelona about foods that have health claims associated with reduced risk of heart disease. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	A combination of the options is appropriate.(1) Provide basic information and counseling related to functional foods with health claims associated with heart disease. Emphasize authorized and authoritative health claims (Table 24-1), because these are supported by strong scientific evidence. The limited evidence for qualified claims and structure-function claims can be presented along with a discussion of where they fit, if at all, in the patient's overall plan.(2) Refer Mrs. Barcelona for cholesterol screening (or perform screening in the pharmacy) and assessment for heart disease.(3) Refer Mrs. Barcelona to a dietitian if her daughter feels she needs more than basic counseling on nutrition, or have her request a referral from her primary care provider (may be necessary for insurance coverage).(4) Weight control and heart disease should be discussed with Mrs. Barcelona, or these issues should be suggested as part of her discussion with her primary care provider or a dietitian.
6. Describe the recommended therapeutic	"A number of foods with health claims are associated with decreased risk of heart disease. For several foods, there is significant scientific agreement regarding their potential benefits. Using these foods in place of some of

approach to the patient or caregiver.	your current foods may reduce your risk of heart disease. However, it also would be helpful to know what your risks are, including your cholesterol level.”
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	“Given your family history, you should have your cholesterol checked periodically and be evaluated for other risk factors for heart disease. Your weight is a risk factor for heart disease for you.”“I can provide you with basic information on foods that have health claims related to heart disease and that may be of benefit in maintaining heart health. Dietitians are the food and nutrition experts; they can do a comprehensive assessment of your diet and provide more in-depth dietary counseling if you want that.”
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	(1) “Decrease the saturated fat and cholesterol in your diet. No more than 10% of your calories should come from saturated fat, and you should limit cholesterol in your diet to no more than 300 mg cholesterol a day, but less is better. When you drink milk, you might want to try 1% milk; most people find that to be more acceptable than nonfat (skim) milk, and it is lower in fat than 2% milk. Or you could try soy or almond milk. Low-fat yogurt also is another good calcium source and usually is tolerated by people with lactose intolerance.”(2) “Eat fruits, vegetables, and grain products that contain fiber, particularly soluble fiber. Replace white breads and pasta with whole-grain products. Total dietary fiber should be at least 25 g daily.” [AI for women 19–50 years of age](3) “You also can get soluble fiber from oat bran, rolled oats, or whole oat flour in certain foods, or from barley. Incorporate these products into the diet as replacement for breads and cereals that are not whole grain.”(4) “Plant sterol and stanol esters also help to reduce the risk of heart disease. Total intake is at least 1.3 g daily of sterol esters or 3.4 g daily of stanol esters, as part of a diet low in saturated fat and cholesterol. You usually need to eat the products at least twice a day to get the recommended amount. Some margarines and orange juice have added plant sterol/stanol esters.”
	(5) “The health benefits of eating whole-grain foods overlap somewhat with those for grain products containing fiber, as noted earlier, but not limited to soluble fiber only. Insoluble fibers also are important in health. Look for whole grains, such as whole wheat, as the first ingredient on labels.”
	“To make these health claims, foods must generally contain a certain amount of the desired component. Check food labels for these claims and for ingredient amounts.”

	“There are also other foods that are considered healthy but do not yet have strong evidence to suggest they help to reduce the risk of heart disease. Therefore, the health claims may not be as effective or the claims might be changed if new studies are reported. Because the following foods are otherwise healthy foods when used in moderation, they can still be safely incorporated into your diet.”
	(1) “Walnuts and several other types of nuts: 1.5 ounces a day; remember that nuts are a concentrated source of calories, so use judiciously.”
	(2) “Omega-3 fatty acids: specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), found in salmon, lake trout, herring, and other oily fish.”
	(3) “Monounsaturated fats from olive oil: 23 g daily (2 tablespoons) in place of a similar amount of saturated fat. A number of salad dressings and a few soft margarines now include olive oil.”
	(4) “Canola oil, unsaturated fatty acids: 19 g daily (1.5 tablespoons) in place of a similar amount of saturated fat. Some cooking oil, a number of salad dressings, a few soft margarines, and some baked goods include canola oil.”
	(5) Oleic acid: 20 g daily (1.5 tablespoons) in place of fats and oils higher in saturated fat. A number of cooking oils, including olive oil, nuts, and avocado, include oleic acid.
	(6) Soybean oil: 20.5 g daily (1.5 tablespoons) in place of a similar amount of saturated fat. Soybean oil is now a popular oil to use for cooking.
Solicit follow-up questions from the patient or caregiver.	(1) “Are there any things I need to be aware of as I add these foods into my diet?”
	(2) “Are there any side effects from changing my diet?”
	(3) “Where can I find more information on dietary changes and diet plans to prevent heart disease?”
	(4) “May I use dietary supplements instead of changing to functional foods? Most information on the Internet is advertising for dietary supplements.”
Answer the patient’s or	(1) “These foods should replace other foods in your diet so that the total calories do not increase. The more ‘healthful’ fats must replace saturated

caregiver's questions.	fats and not increase the total fat intake. You will need to read food labels carefully to be sure you are getting whole grains, low saturated fats, low cholesterol, and sterol/stanol esters in the product. Also look for the amount of soy or soluble fiber."
	(2) "Rapid increases in fiber content of the diet can cause gas and bloating, so it is best to gradually increase the fiber in your diet. Replace 1-2 servings of white bread and pasta with whole-grain products every few days until the refined foods are totally replaced. Also add extra fiber by gradually replacing the low-fiber cereals with a whole-grain cereal or oatmeal. Fruits and vegetables can be increased gradually as well to replace snacks and desserts. Be sure to drink plenty of water when eating a high-fiber diet."
	(3) "The U.S. Food and Drug Administration website (www.fda.gov) includes information on health claims and food labels that you might find helpful. You could consider making an appointment with a registered dietitian, who could help develop some menus that incorporate foods you like and provide more specific plans for substituting healthier foods. Your health insurance plan may contract with a dietitian for coverage. If not, the Academy of Nutrition and Dietetics can provide the name(s) of private consultants and the contact information for a dietitian. The phone number for referrals is on their website (www.eatright.org)."
	(4) "In general, foods are better than supplements. Many studies have shown beneficial effects from a diet containing fiber-rich foods and whole grains but not with isolated supplements. Psyllium, found in products like Metamucil, fits criteria for a health claim related to soluble fiber and risk of congestive heart disease and could be used to increase soluble fiber. It also has the added benefit of reducing constipation, as do fibers from whole grains."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	"May we talk about the changes you have made in your diet when you pick up your prescription refills next month?"

Medical Foods and Meal Replacement Foods

Traditional medical foods include products developed for patients with inborn

errors of metabolism (“metabolics”). Product descriptions are available on manufacturer websites, and such products may be available from the federally funded Special Supplemental Nutrition Program for Women, Infants, and Children (WIC), because this program is often involved in distribution of products and patient monitoring. Enteral nutrition formulas, specialty formulas in particular, may meet the definition of a medical food; however, many such products are better classified as food for “special dietary use,” because they are readily available for purchase without a medical recommendation or prescription and are marketed directly to consumers as regular foods, often as meal replacement products. Enteral formulas typically are semisynthetic liquid formulas intended for oral consumption or administration through a feeding tube. Certain liquid diets designed for use in medically supervised very-low-calorie diets or bariatric programs are classified as medical foods. Various puddings, shakes, and other solid or semisolid food forms specially formulated and processed to meet *distinctive* nutritional requirements of the disease or condition for which they are intended also can be classified as medical foods. Both liquid and solid medical foods may replace regular meals or enhance nutrient intake to meet the distinctive nutritional requirements of patients. However, these products also are frequently used to meet general nutritional needs.

Health care providers involved with self-care counseling should determine when a product is used as a medical food to meet truly distinctive nutritional requirements, as determined by scientific studies, and when it is used as meal replacement or enhancement to meet *general* nutritional requirements. Foods intended to meet general nutritional requirements do not need medical oversight and can be used safely for self-care. By contrast, FDA regulations state that use of medical foods requires recommendation or prescription by a physician or other authorized prescriber *and* ongoing medical supervision.^{4,16} Referral to a dietitian generally is appropriate for patients with distinctive nutritional requirements. When enteral formulas are used to meet general nutritional requirements, however, third party providers may refuse to cover the cost under insurance benefits, leaving patients with self-care responsibility.

Enteral Formula Uses

Tube Feeding

Enteral formulas are best known as complete nutritional replacements for patients requiring a feeding tube to meet their nutritional needs, such as persons with severe dysphagia subsequent to a stroke. Patients who cannot, should not, or will not take adequate nutrients by mouth are candidates for tube feeding and should be under medical care; tube feeding is not a condition conducive to a safe and effective self-care approach. Unfortunately, little if any support is provided by most suppliers of adult enteral formulas in today's health care environment, even if the formula itself is covered by insurance benefits. Patients in this situation may benefit from referral to a Certified Nutrition Support Clinician (CNSC) or Board Certified Nutrition Support Pharmacist (BCNSP) if they are experiencing any difficulty with their feedings. For information related to tube feeding, the reader is referred to one of the many specialized references available; to the Oley Foundation (www.oley.org), a consumer-oriented organization for support of people requiring intravenous or tube feeding; or to the American Society for Parenteral and Enteral Nutrition (ASPEN). In addition to topics related to enteral and parenteral nutrition, the ASPEN website (www.nutritioncare.org) contains literature and other resources related to malnutrition.

Many enteral preparations are currently available. Most formulas provide nutritional support consistent with general dietary guidelines and are safe for use in self-care. Formulas intended for patients with impaired digestion and those designed for specific metabolic or clinical conditions require oversight by a qualified health care provider. Characteristics that are likely to result in the use of a formula as a true medical food requiring medical supervision are listed in **Table 24–8**, along with a few representative products. The patient's overall health condition also influences the need for medical supervision. For example, formulas with >25% of calories from protein should be used with medical supervision in patients with compromised renal function, but the potential for adverse effects is of less concern when these products are used occasionally by people with normal renal function.

Table 24–8 Enteral Formula Characteristics Consistent With Need for Medical Supervision

Characteristic	Example(s)
Protein as peptides and/or free amino acids	Peptamen, Crucial, Vital

Characteristic	Example(s)
Alteration of amino acid content by addition of individual amino acids, such as glutamine, arginine, or branched-chain amino acids	Juven, Impact, Perative
Addition of specific fatty acids to alter the inflammatory response	Oxepa
Addition of significant amounts of medium-chain triglycerides to alter absorption	Portagen, Enfaport
High percentage (>50%) of calories from fat	Pulmocare
Very high protein content (≥25% of calories as protein)	Nutren Replete, Promote
Intended for patients with organ failure	Renalcal, Nepro, Suplena with Carbsteady, NutriHep

Supplementation of Nutrient Intake

Liquid food preparations, including enteral products initially developed for tube feeding, are often used as oral supplements. They frequently are marketed directly to consumers as supplements to the usual diet and as convenience foods to meet general nutrient goals, most commonly for protein, calories, or both. Older adults tend to be a major target for use of such products because of changes related to aging ([Table 24–9](#)) that may contribute to reduced oral intake and increased risk for malnutrition.^{52–55} Products also are marketed as “meal replacement” alternatives that are healthier than eating “fast foods” or skipping meals and that serve as a method of portion control. Persons participating in sports activities are targeted for selective products (see [Chapter 25](#)).

Oral nutritional supplements (ONS) benefit hospitalized patients who are undernourished at baseline; use of such products also is recognized to reduce hospital readmissions.^{53,55,56} A systematic review and meta-analysis conducted in the United Kingdom reported a reduction in readmissions from 33.8% to 23.9% with use of ONS compared with standard care; the number needed to treat was 10.⁵⁵ Benefit from routine ONS use at home or for persons who are well nourished in any setting is more difficult to demonstrate. However, reported prevalence rates for malnutrition among community-dwelling older adults living in industrialized nations vary, with a range of 7%–35%, depending on the criteria used to define malnutrition and the settings included.⁵⁴ Of chronically ill community-dwelling patients in the United States, 10% have

disease-associated malnutrition.⁵⁷ The cost of community-based disease-associated malnutrition in the United States is estimated to be \$157 billion based on 2010 dollars, with more than 75% of expenditures associated with increased morbidity. In addition, evidence is mounting for the need for higher protein intake among all older adults to maintain physical function and mitigate risk for sarcopenia, osteoporosis, and impaired immune response.⁵³ Unfortunately, physicians and other health care providers typically receive minimal training in nutrition, and malnutrition often is not addressed until patients are significantly malnourished. Patients and families may therefore seek self-care alternatives, including ONS, to improve nutritional intake and mitigate or prevent malnutrition. Growing evidence indicates that ONS can be useful to prevent malnutrition.^{53,55,56} These ONS products may or may not be complete (i.e., contain all necessary nutrients, including vitamins and trace elements) and balanced (i.e., contain appropriate ratios of nutrients) in their nutritional content. Users of such products should carefully review labels to ensure that their overall diet is complete and balanced.

Table 24–9 Changes With Aging and Other Factors That May Contribute to Poor Oral Intake and Malnutrition

Gastrointestinal Tract Changes
Reduced taste threshold
Motility dysfunction of lower esophageal sphincter
Slowed gastric emptying
Reduced gastric acid production
Decreased number and density of nerve fibers in the myenteric plexus
Impaired renewal and regeneration of intestinal epithelial tissue
Decreased number of Brunner glands in the duodenum resulting in a lower pH, which impairs pancreatic enzyme function
Colonic motility dysfunction resulting in either constipation or fecal incontinence
Structural changes in the pancreas
Decreased pancreatic lipase
Reduced gut-associated lymphoid tissue (GALT) immune response

Changes That Affect Protein Requirement and Intake
Reduced anabolic response to ingested protein
Impaired antiproteolytic response to insulin
High splanchnic protein extraction
Increased inflammatory and catabolic conditions
Other Factors
Poor appetite
Edentulousness
Self-reported poor health
Hospitalization

Source: Adapted from [References 52–55](#).

Classification of Enteral Nutrition Products

Enteral products are classified as polymeric formulas, oligomeric formulas, and modular components. In addition, a growing segment of meal supplement and meal replacement products, including beverages, bars, and puddings, are designed to assist in meeting nutrient goals within an appropriate caloric intake.

Polymeric Formulas

Polymeric formulas are used most often. They are for people with normal digestive capability and contain macronutrients in the form of intact (whole) proteins, carbohydrates, and fatty acids or oils. Most persons who require alternative nutrition support will tolerate and do well with standard polymeric formulas. The standard formulas usually (1) supply 1 kcal/mL unless concentrated to provide less free water; (2) feature a macronutrient composition typical of the American diet (carbohydrate: 45%–70%; protein: 10%–18%; fat: 20%–40%); and (3) are isotonic to slightly hypertonic with respect

to body fluids (300–450 mOsm/kg); however, the osmolality of flavored products often ranges from 500 to 700 mOsm/kg. Polymeric formulas are listed as being generally safe for self-care when taken orally ([Table 24–10](#)).

Table 24–10 Examples of Meal Replacement Products/Liquid Formulas Suitable for Self-Care^a

Product Name	Energy (kcal/mL)	Protein (g [% kcal])^b	CHO (g [% kcal])	Fat (g [% kcal])	Fiber (g)	Use as Sole Source of Nutrition?	Comments
Routine Formula							
Boost (Original)	240 (1.0)	10 (17%)	41 (68%)	4 (15%)	3	Yes	PREBIO prebiotic fibers
Ensure	220 (0.93)	9 (16%)	32 (58%)	6 (25%)	None	Yes	
Routine Formula With Extra Protein							
Boost High Protein	240 (1)	15 (25%)	33 (53%)	6 (22%)	None	Yes	
Boost Optimum	220 (0.9)	22 (40%)	19 (35%)	6 (25%)	None	No	
Ensure High Protein	160 (0.67)	16 (40%)	19 (48%)	2 (11%)	None	No	
Ensure MAX protein	150 (0.45)	30 (80%)	6 (16%)	1.5 (9%)	2	No	11-ounce (330 mL) serving package
Carnation Breakfast Essential High Protein Ready-to-Drink	220 (0.9)	15 (27%)	28 (48%)	6 (25%)	3	No	PREBIO prebiotic fibers
Routine Concentrated (High-Calorie) Formula							
Boost	360	14 (15%)	45	14	3	Yes	PREBIO prebiotic

Product Name	Energy (kcal/mL)	Protein (g [% kcal])^b	CHO (g [% kcal])	Fat (g [% kcal])	Fiber (g)	Use as Sole Source of Nutrition?	Comments
Plus	(1.5)		(50%)	(35%)			fibers
Ensure Plus	350 (1.5)	13 (15%)	50 (57%)	11 (28%)	None	Yes	
Diabetic Formula^c							
Boost Glucose Control	190 (0.8)	16 (33%)	16 (34%)	7 (33%)	3	No	Added L-arginine; Nutrisource fiber; Equals 1 carb choice
Glucerna Shake	180 (0.76)	10 (22%)	16 (36%)	9 (45%)	4	No	Carbsteady blend of slow-release CHO
Glucerna Shake Advance	200 (0.84)	10 (20%)	27 (54%)	7 (32%)	3	No	CarbsteadyUltra advanced blend of slow-release CHO; Heart healthy omega-3 fatty acids and phytosterols
Glytrol	250 (1)	11(18%)	25 (40%)	12 (42%)	3.8	No	PREBIO prebiotic fibers
Other Meal Replacements and Supplements							
Ensure Clear	180 (0.6)	8 (18%)	37 (82%)	None		No	10-ounce (296 mL) serving package; clear liquid
Boost Breeze	250 (1.06)	9 (14%)	54 (86%)	None	None	No	Clear liquid
Carnation Breakfast Essential Powder Drink Mix	220 (0.8)	13 (23%)	39 (74%)	1 (3%)	<1	No	Mix 1 packet in 1 cup fat free milk; mixing with 2% or whole milk increases calories as fat. Can mix with soy milk or

Product Name	Energy (kcal/mL)	Protein (g [% kcal])^b	CHO (g [% kcal])	Fat (g [% kcal])	Fiber (g)	Use as Sole Source of Nutrition?	Comments
							reduced lactose milk.
Carnation Breakfast Essential Ready-to-Drink	240 (1)	10 (17%)	41 (68%)	4 (15%)		No	
Modular Components^d							
Bene-protein	25	6 (100%)	None	None	None	No	Listed content per 7 g packet or 1 scoop
ProMod Liquid Protein	100 (3.33)	10 (40%)	14 (60%)	None	None	No	Listed content per ounce (30 mL); curdles when mixed with enteral formula
Bene-calorie	330 (7.5)	7.5 (9%)	None	33 (91%)	None	No	Content per 1.5-ounce serving (44 mL)
Micro-lipid	67.5 (4.5)	None	None	7.5 (100%)	None	No	Content per 15 mL; 50% fat emulsion; safflower oil
Nutri-Source Fiber	15	None	4 (100%)	None	3	No	Content per 4 g serving; 100% soluble fiber

Note: The most current and detailed information is available at manufacturer websites, including Abbott Nutrition (www.abbottnutrition.com/brands) and Nestlé Nutrition (<https://www.nestlehealthscience.us/>).

^a Amounts are for an 8-ounce serving unless otherwise indicated. Some products are listed for use under medical care; however, the products meet nutritional content

consistent with general dietary guidelines, unless otherwise indicated, and can be used for self-care. The products can be obtained in consumer-size single-serving packages (8–12 ounces) without a prescription and are available through the Internet or retail businesses.

^b Protein content over 25% of calories should generally be used as a supplement to oral intake. Use as a sole source of nutrition should be under medical supervision even when a formula is listed as complete.

^c Use sparingly for self-care, because the fat content is relatively high compared with that in studies of high-fat/low-carbohydrate diets and is higher than that recommended by general dietary guidelines. In accordance with recommendations from the American Diabetes Association (www.diabetes.org; see American Diabetes Association, Bantle JP, Wylie-Rosett J, et al. Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. *Diabetes Care*. 2008;31(Suppl 1):S61–78), monounsaturated fatty acid content tends to be higher than in many standard formulas, and saturated fat content is low. Products should be used as part of a diabetes management plan, which does require medical supervision.

^d Modular components can be added to food or mixed with water and flushed through a feeding tube. Modular components generally should not be added directly to the enteral formula.

Key: CHO = Carbohydrate.

Oligomeric Formulas

Oligomeric products require minimal digestion and also are known as predigested, peptide, or elemental formulas. They contain free amino acids, hydrolyzed or partially hydrolyzed protein, and less-complex carbohydrates. In these formulas, the fat content frequently is altered to improve absorption if impaired. Oligomeric formulas most often are used in the acute care setting when a polymeric formula has proved inadequate or for initial nutritional support for patients in whom malabsorption is likely because of critical illness, recent surgery, severe malnutrition, or exacerbation of gastrointestinal disease (e.g., Crohn disease). They are rarely consumed orally because of poor palatability. In general, use of oligomeric formulas requires medical supervision.

Modular Products

Modular products supplement a single macronutrient. Examples are protein powder, medium-chain triglyceride oil; emulsified oils, and powdered, flavorless glucose polymers. These products can be incorporated into food to increase protein and calorie content. For example, a protein powder may be of benefit in an older adult who is having difficulty meeting protein requirements with the usual oral diet.

Specialty Formulas

Specialty formulas may be either polymeric or oligomeric. They are designed to optimize nutrient intake and improve disease management for patients with specific disease states such as renal insufficiency, diabetes mellitus, hepatic dysfunction, and carbon dioxide–retaining pulmonary dysfunction. The use of specialty formulas is controversial; data supporting improved outcomes are limited. In general, use of such formulas requires medical supervision. Consultation with a registered dietitian, CNSC, or BCNSP may be warranted.

Immune-modulating formulas contain components such as arginine, glutamine, omega-3 fatty acids, dietary nucleotides, and/or antioxidants. They most often are used perioperatively in the acute care setting; however, oral consumption of an immune-modulating formula may be recommended for a specific period before and after major elective surgery in some patients. This use does not qualify as ordinary self-care and should be monitored by a qualified health care provider. Further information and guidelines related to immune-modulating formulas are available from nutrition support organizations, such as ASPEN ([nutritioncare.org](https://www.nutritioncare.org)).

Some specialty formulas, such as certain pulmonary and diabetic formulas, supply different ratios of fat and carbohydrate but contain no special dietary components. Although technically such products are medical foods, most people who use them could replace a few meals per week with little concern for adverse effects. However, patients must be encouraged to limit their use unless otherwise advised by a qualified health care provider or a specialist in nutritional management of their condition. In any case, meal replacement with such products should be reported to the primary care provider, because management of the underlying disease itself requires medical oversight. [Table 24–10](#) includes a few examples of pulmonary and diabetic formulas.

Product Use for Self-Care

All products recommended for self-care, whether initially marketed for tube feeding or intended for oral ingestion, should contain basic nutrition labeling, including serving size, calories, protein, fat, and other components consistent with food labeling so that nutrient intake can be determined in the same manner as for regular foods. Many formulas are available in a variety of flavors to reduce taste fatigue; nutrient content may differ slightly among the flavors.

Administration and Monitoring Guidelines for Enteral Nutrition

For products taken orally, the patient should be encouraged to vary flavors to avoid taste fatigue and to consume the product after an attempt to eat a well-balanced meal or a between-meal snack. Chilling may improve palatability. Once opened, the container should be kept refrigerated to prevent bacterial growth, and all open or prepared products should be discarded after 24 hours.

When products are given as tube feedings, medical supervision is recommended. Enteral nutrition practice recommendations are available at the ASPEN website (www.nutritioncare.org). Referral to a nutrition support provider may be appropriate. Medical referral is appropriate for patients in whom consumption of meal replacement formulas leads to development of diarrhea, nausea, or abdominal distention. Formula-related diarrhea is an osmotic diarrhea that usually stops within 24 hours of discontinuing the formula; diarrhea that persists longer is unlikely to be caused by the formula per se. Lactose intolerance is seldom an issue with enteral formulas; most formulas, except powders prepared with milk, are lactose-free. Other products not intended for tube feeding, however, may contain lactose. Many high-protein products marketed for oral consumption by the general population contain milk proteins (whey and/or casein), although they are lactose-free. High-fat products can delay gastric emptying, resulting in nausea and/or abdominal bloating.

Food–Medication Interactions

Interactions between medications and enteral formulas often are complex and

poorly understood. Interactions involving a formula component have the potential to occur with either oral administration or feeding tube administration. The health care provider is advised to consult specialty references for a more complete listing and explanation of such interactions. Although controversial, general practice with administration of certain medications (including phenytoin, carbamazepine, and warfarin) is to withhold the tube feeding formula for 1 or 2 hours before and after giving the medication, especially when therapeutic levels are not achieved with typical doses. It is reasonable to suggest this same precaution of separating drug administration by 1 or 2 hours when formula is taken by mouth and to advise supervision of the medication response by a primary care provider. Vitamin K content of the formula also should be checked for patients on warfarin. Although most formulas provide no more vitamin K than that of a typical diet, a few contain this vitamin in amounts that could interfere with anticoagulation. Manufacturers' websites, such as those listed in the footnotes in [Table 24–10](#), provide detailed, up-to-date information on the nutrient content of formulas.

Other Medical Foods and Meal Replacement Foods

In recent years, several medical foods have become available for a range of common diseases treated in the ambulatory care setting ([Table 24–11](#)). Foods used in weight loss and bariatric programs also are medical foods for which medical supervision is required with use as intended, because of the significant risks associated with rapid weight loss. Meal replacement foods such as Slim Fast, Weight Watchers, and Jenny Craig products are not medical foods. They can be used safely without medical supervision to help control portion size and to balance nutrient intake; however, they should be used as part of an overall weight loss plan (see [Chapter 27](#)).

Assessment of Enteral Nutrition and Meal Replacements: A Case-Based Approach

The first step in assessing the type of meal replacement (or supplement) to

recommend is to determine the presence of any of the exclusions for self-care listed in [Table 24–12](#). If self-care is permissible, the provider should ascertain the reason for a meal replacement or supplement so that the most appropriate product can be selected. For instance, an older adult with early satiety may benefit from a concentrated formula that provides 1.5 or 2 kcal/mL, whereas for a young person seeking a meal supplement for use with weight lifting, a higher protein formula may be more appropriate. The selected formula should meet the patient’s specific nutritional needs according to health status while avoiding excessive or contraindicated macronutrients and micronutrients.

Table 24–11 Examples of Products Marketed as Medical Foods for Common Conditions

Condition	Product(s) [Alternate Name] (Manufacturer)
Alzheimer disease	Axona (Accera, Inc.)
	Cerefoli Nac [metafolbicplus] (Alphasigma USA, Inc.)
Attention deficit hyperactivity disorder (ADHD)	Vayarin (VAYA Pharma, Inc.)
Depression	Deplin [levomefolate] (Alphasigma USA, Inc.)
Depression-associated sleep disorders	Sentra PM (Targeted Medical Pharma)
	GABAdone (Targeted Medical Pharma)
Diabetic neuropathy	Foltanx (Breckenridge, Inc.)
	Metanx (Alphasigma USA, Inc.)
Dyslipidemia	UltrMeal Cardio 360° (Metagenics)
Fatigue and cognitive disorders	Sentra AM (Targeted Medical Pharma)
Inflammatory bowel disease–associated gut dysfunction	UltrInflamX Plus 360° (Metagenics)
Irritable bowel syndrome	VSL#3 probiotic (Sigma-Tau Pharmaceuticals)
	Enteragam (Entera Health, Inc.)
Osteoarthritis	Limbrel (Primus Pharmaceuticals)

Condition	Product(s) [Alternate Name] (Manufacturer)
Osteopenia/osteoporosis	Fosteum Plus (Primus Pharmaceuticals)
Pain and inflammation	Theramine, for chronic pain (Targeted Medical Pharma),
	Trepadone, for joint disorders (Targeted Medical Pharma)
	Percura, for peripheral neuropathy-associated pain and loss of sensation (Targeted Medical Pharma)
Sarcopenia	UltraMeal Advanced Protein (Metagenics)
Ulcerative colitis	VSL#3 probiotic (Sigma-Tau Pharmaceuticals)

Table 24–12 Exclusions for Self-Care With Enteral Formulas

Condition	Example/Comments
Organ dysfunction requiring diet modification	Renal insufficiency requiring restriction of protein and electrolytes eliminated through the kidneys (potassium, phosphorus, magnesium)
Gastrointestinal dysfunction	Poor motility: Dietary modification may be required to avoid bowel obstructions; enteral formula may be appropriate under the supervision of a PCP or nutrition specialist; use for self-care is not appropriate.
	Reduced absorption: Hydrolyzed protein, modified fats, and/or relatively simple carbohydrates may be necessary for adequate absorption; monitoring for nutrient deficiencies is required.
	Dysphagia: Referral for medical evaluation is required.
	Bariatric surgery: Medical supervision is required; recommendations of a PCP or nutrition specialist should be followed.
Significant unintended weight loss	Refer for medical evaluation to determine the underlying cause.
	Life-threatening fluid and electrolyte abnormalities can occur when refeeding affected persons; medical supervision and monitoring are required.
Disease state affected by diet, such as diabetes	Enteral formula may be appropriate to meet nutritional requirements; use should be under the supervision of a PCP or

Condition	Example/Comments
mellitus, chronic obstructive pulmonary disease	nutrition specialist; use for self-care is not appropriate.

Key: PCP = Primary care provider.

Meal replacement products can have efficacy for the treatment of many health concerns. Traditionally, meal replacement has been considered a therapeutic intervention needed to maintain adequate nutrition in malnourished patients; to completely replace nutritional intake in patients with a physical limitation that interferes with nutritional intake (e.g., dysphagia); or to precisely control intake of specific dietary components (calories for obesity and phenylalanine in phenylketonuria). Increasingly, nutrition products are used as lifestyle choices of self-directed therapy. This practice is particularly true of the meal replacement products used by working people who are too busy to prepare or eat a proper meal or who perceive these products as healthier alternatives to fast foods.

Case 24–2 illustrates assessment of a patient with Alzheimer disease for whom a food/liquid meal product seems indicated.

Case 24–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	

a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient is an older adult with progressive Alzheimer dementia symptoms. Her daughter reports that the patient is easily frustrated and demanding of attention.
	The daughter also describes her as being very forgetful, asking the same question every 5 minutes and being very upset that she is not getting an answer despite her daughter's answering each time. Signs of dementia have worsened in the past month. At the Alzheimer family support meeting last week, the daughter heard about a food/liquid meal that is helpful in slowing the disease's progression, and she is requesting this product for her mother.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	n/a
c. Description of the patient's efforts to relieve the symptoms	Patient is currently taking a combination product containing donepezil and memantine (changed a month ago from donepezil). She also takes a "senior" multivitamin/mineral supplement.
d. Patient's identity	Sophia Valdez
e. Patient's age, gender, height, and weight	82 years, female, 5 ft 1 in., 100 lb
f. Patient's occupation	Homemaker
g. Patient's dietary habits	Usually has two meals daily and a couple of snacks. Must be reminded to eat and encouraged to eat more than one food off her plate; sometimes she refuses to eat anything.
h. Patient's sleep habits	Sleeps about 6 hours at night but also naps during the day.
i. Concurrent medical conditions, prescription and	Hydrochlorothiazide for hypertension; multivitamin/mineral supplement

nonprescription medications, and dietary supplements	
j. Allergies	No known medical allergies
k. History of other adverse reactions to medications	Ataxia with metronidazole
l. Other (describe) -----	n/a
Assess	
2. Differentiate patient's signs/symptoms and correctly identify the patient's primary problem(s).	Patient's daughter is requesting a medical food for use in Alzheimer dementia.
3. Identify exclusions for self-treatment (Table 24-12).	Medical foods require medical supervision.
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer patient to her regular health care provider to discuss use of the medical food and to obtain a recommendation. (2) Recommend self-care with a general supplement to improve nutrient intake. (3) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into	Patient's daughter should consult with her mother's primary care provider regarding the medical food.

account patient preferences.	
6. Describe the recommended therapeutic approach to the patient or caregiver.	“You are requesting a product that requires medical supervision for use. The pharmacy can order the product for you once you have discussed this with your mother’s health care provider and you have a recommendation.”
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	“In addition to verifying that your mother has medical supervision for using the product, a prescription may make the product eligible for coverage by your mother’s insurance, although such products typically are not covered.”
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	Criterion does not apply in this case.
Solicit follow-up questions from the patient or caregiver.	“Do you know how this product works, and could I just change what I cook for my mother rather than discussing her eating problem with her provider? I thought this product would also help with her calorie intake, as she has lost 7 or 8 pounds in the last couple months, because she often refuses to eat at mealtime. She will drink a milk shake when I’m home to make one in the afternoon, but I’m at work most afternoons. Is there a product that I could use instead that would also increase her daily calories?”
Answer the patient’s or caregiver’s questions.	“The medical food product for Alzheimer disease is based on a specific type of fat that is absorbed and metabolized differently than the typical oils found in the grocery store. It must be given in an appropriate amount with a proper balance of other nutrients to achieve the desired effect. Your mother’s weight loss is concerning

	and should be evaluated by her primary care provider to be certain the weight loss is related only to not eating enough; it could be related to a medical condition that requires treatment.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	“Let me know when you have discussed these issues with your mother’s primary care provider. If you decide to try the medical food for Alzheimer disease, I can order the product once you obtain the recommendation, and preferably a prescription for documentation of medical supervision. If you want more information on the product, you also can check the product manufacturer’s website (www.about-axona.com). The Alzheimer’s Association website (www.alz.org) also has information on current research, alternative therapies, and their evaluation of various types of products marketed for Alzheimer disease.”
	“A prescription is not required for most liquid meal products intended to supplement calories, and I can help you select a product if your mother’s regular health care provider thinks her weight loss is primarily due to inadequate food intake. You also may want to ask your mother’s provider about a nutrition consultation, because a dietitian or nutrition support specialist could provide a more complete nutritional assessment as well as more comprehensive recommendations related to her diet.”

Patient Counseling for Enteral Nutrition and Meal Replacements

Advancements in home infusion therapy, along with development of an increased range of enteral products, are allowing more people with serious, even terminal, illnesses to be cared for at home. Enteral products also are appropriate for ambulatory patients with metabolic or digestive diseases and for persons who want to ensure adequate nutrition for their life stage. Providers serve a pivotal role in helping patients to select the optimal product for their nutritional needs and to assist them in its proper use, under medical supervision when indicated. The box “Patient Education for Enteral and Meal Replacement Products” lists specific information to provide patients and

Patient Education for Enteral and Meal Replacement Products

The objective of self-treatment is to provide the appropriate amounts and types of specific micronutrients and macronutrients to meet the person's nutritional needs. For most people, the product instructions and self-care measures listed here will help ensure optimal therapeutic outcomes.

- Typical products provide 1 Kcal/mL; higher-calorie products are available if you must limit your fluid intake or can drink only a small amount at a time.
- When drinking the formula, take about ½–1 can/container at a time. You can drink the formula at room temperature, but it may taste better if chilled or semifrozen as a slush-type drink.
- Varying the flavor of the formula may reduce taste fatigue.
- For tube feeding, the product should be used as directed by your primary care or nutrition care provider. The Oley Foundation (www.oley.org) provides consumer information on tube feeding.
- Keep opened containers refrigerated and covered to prevent bacterial growth; discard all remaining prepared products after 24 hours. Unopened product can be stored at room temperature.
- Use of meal replacement products as the sole or primary source of nutrition for longer periods of time (>3 weeks) requires medical supervision and should be discussed with your primary care provider. Periodic laboratory testing may be appropriate to detect electrolyte abnormalities in this situation.

When to Seek Medical Attention

- Monitor blood glucose (sugar) levels if you have diabetes or have had high blood glucose levels. Talk to your primary care provider if your blood glucose levels are high or low.

Key Points for Functional and Meal Replacement Foods

- The definition of FF typically includes providing “health benefits beyond those of basic nutrition.”
- Health claims are statements describing an association between a food, food component, dietary ingredient, or dietary supplement and the risk of a disease or health-related condition.
- Authorized and authoritative health claims meet the significant scientific agreement level of evidence. These claims should be routinely incorporated into counseling for lifestyle changes associated with health benefits and, when appropriate, included as part of an overall plan for management of diseases associated with these claims.
- Qualified health claims do not meet the significant scientific agreement level of evidence; a claim statement must include language that indicates the qualified nature of the health claim.
- Structure–function claims lack the significant scientific agreement level of evidence and make no association between the product and the risk of a disease or health-related condition; they do not require validation or authorization by FDA.
- Health care providers should understand the limitations of qualified health claims and structure–function claims. In counseling for lifestyle changes, the limited scientific evidence for these claims should be clearly delineated so that patients can understand the role, or lack thereof, for these products in a healthy lifestyle.
- Foods for special dietary use meet particular dietary needs related to physical, physiologic, pathologic, or other conditions, such as disease, convalescence, pregnancy, lactation, underweight, overweight, infancy, or need for sodium restriction, or are used to supplement or fortify the usual diet. They are subject to general

labeling requirements for foods and do not require use under medical supervision.

- Medical foods are specially formulated and processed to meet distinctive nutritional requirements (established by medical evaluation based on recognized scientific principles) of the disease or condition for which they are intended. These foods are to be recommended and used under medical supervision.
- Conventional foods classified as FF typically are associated with health benefits in epidemiologic studies; evidence supporting a functional role for these foods is weak–moderate, with clinical trials often lacking.
- Fiber is associated with improved laxation, cholesterol reduction, satiety, and probably glucose control for select fiber sources.
- Enteral nutrition products may be classified as medical foods; however, many polymeric enteral formulas are readily available and often can be used safely as a meal replacement product.
- Specialty enteral formulas should be used with medical supervision, not for self-treatment.
- Semisynthetic liquid formulas intended for oral consumption may or may not be complete and balanced nutritional products.
- Nutrient content of meal replacement products should be considered in evaluating dietary intake to ensure that the overall dietary content is complete and balanced.

Chapter 25: Sports Nutrition and Performance-Enhancing Nutrients and Supplements

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Recreational athletes exercise at a variety of intensities but usually target general health, wellness, or stress reduction as an intended outcome. Such recreationally active people typically perform less than 1 hour of activity per session and usually engage in only 3–4 sessions each week. The Academy of Nutrition and Dietetics would classify this group of athletes, who are active less than 7 hours per week, as low-volume exercisers.¹ Diet alone should meet their nutritional needs. By comparison, athletes in a program of moderate training for 7–20 hours per week or high-volume intense training for greater than 20 hours per week may require specific nutritional intake to maintain or enhance performance.¹ This chapter provides an introduction to the effects of products that contain macronutrients and nutritional supplements on physical activity and performance for both the recreational athlete and the more aggressive competitor.

Certain food supplements and natural products are marketed as ergogenic aids to athletes and other active people for three primary purposes: (1) to improve strength and power, (2) to prolong the duration of exercise by providing fuel for continued effort, and (3) to replace water and electrolytes lost in sweat with exercise, thus preventing dehydration and supporting normal muscle contractions. Detailed discussions on this topic are available in published guidelines from both the International Society of Sports Nutrition (ISSN) Exercise and Sport Nutrition Review² and a joint statement of the Academy of Nutrition and Dietetics, the Dietitians of Canada, and the American College of Sports Medicine (this collaboration is referred to collectively as “the Academy” in the remainder of this chapter).¹ Sports nutrition is a complex field. Highly competitive and elite athletes who seek advice about sport-specific nutrition or ergogenic aids should be referred to a clinical dietitian with a subspecialty in sports nutrition.

Popularity of Sports Nutrition Products

Sports nutrition products and performance-enhancing supplements have gained wide acceptance in both highly trained athletes and mildly to moderately active people. Increasing numbers of consumers are choosing sports nutrition products as lifestyle alternatives to traditional beverages and snacks. In 2015, the sports nutrition market was estimated to reach \$16 billion in sales worldwide.³ The market segment includes traditional carbohydrate and electrolyte sports drinks, along with energy drinks with supplemental caffeine; recovery drinks; and other nutrient-enhanced soft drinks, juices, and waters. The market for solid forms includes meal replacement bars and easy-to-digest carbohydrate gels. Tablets, capsules, and powders that contain macronutrients, electrolytes, and herbal supplements also are included in the supplement market.

Use and Regulation of Performance-Enhancing Supplements: Labeling and Antidoping Considerations

The U.S. Food and Drug Administration (FDA) does not approve dietary supplements or validate claims of athletic performance enhancement. Reports of nutritional supplement misbranding are common, however, and use of misbranded supplements can result in doping violations within a sport.⁴⁻⁶ *Misbranding* is a lack of correlation between ingredient claims and the actual contents. Misbranded products may contain an ingredient that is not listed on the nutrition facts, or a listed ingredient may not even be present. Misbranded products may also occur when the quantity of an ingredient is significantly more, or less, than the labeled quantity. Unlabeled doping substances, including stimulants and anabolic steroids, were found in 19% of vitamin and creatine supplements submitted for voluntary testing by Olympic athletes in 2002.⁴ An even higher percentage of misbranding was reported in “black market” supplements confiscated by Norwegian authorities and tested by the Norwegian Control Doping Laboratory.⁵ Of the 296 products seized, 80% contained prohibited substances, including anabolic-androgenic steroids, glucocorticoids, antiestrogens, cannabinoids, and other drugs. A recent summary of publications from the period 2000–2017 found frequent misbranding among the supplements tested, with reported contamination rates of 12.5%–58%.⁶ This large review included observational studies in which

human volunteers underwent blood and urine testing after ingestion of various nutritional supplements. In several instances, prohibited substances were identified in the blood and urine samples. These findings suggest that the use of misbranded substances while in competition may lead to doping violations.⁶

The World Anti-Doping Agency states clearly in its Anti-Doping Code that “*Athletes are responsible for any Prohibited Substance or its Metabolites or Markers found to be present in their Samples.*”⁷ A positive test result is a violation regardless of the athlete’s intent or the package label, even when the source can be traced to a nutritional supplement.⁷ Nutritional products are tested at independent laboratories such as ConsumerLab.com, which provides reports for a fee. A list of banned substances and antidoping resources is available from both the U.S. Anti-Doping Agency (at www.usantidoping.org) and the World Anti-Doping Agency (at www.wada-ama.org). Results of independent product testing for banned substances and misbranding are reported by ConsumerLab.com (at www.consumerlab.com), which receives no industry funding. Chapter 50 provides a more detailed discussion of dietary supplement regulation.

Dietary supplements and prescription drugs are used and shared among college and high school athletes, possibly for performance gains. In 2017, the National Collegiate Athletic Association (NCAA) surveyed 23,000 athletes who participated in sports at division I, II, and III levels.⁸ The NCAA survey reported that student athletes were just as likely to use a protein supplement (41%) as they were to take a general multivitamin supplement (41%) in the past 12 months. The report also indicated that 31% of student athletes were using energy boosters (e.g., energy drinks, energy shots) and 13% were using creatine products. Many of today’s high school athletes also are occasional or regular consumers of nutritional supplements.⁹ A survey of American high school athletes published in 2007 noted a high rate of nutritional supplement use: 62.1% used a daily multivitamin, 31.2% used energy drinks, 21.8% used protein powders, and 12.2% used creatine. Among female athletes, 18.6% of seniors reported using a thermogenic substance or “fat burner,” to boost metabolism and lose weight. Of the male students, 5.9% reported using an anabolic steroid. High school athletes reported greater use of these substances compared with college-age students; accordingly, education on the safe and effective use of nutritional intervention, supplements, and performance-enhancing products is needed as early as the high school years.

The American Academy of Pediatrics (AAP) has determined that the average child engaged in routine physical activity should drink water for hydration. AAP has taken the position that carbohydrate-containing sports drinks are not necessary in school sport activities, and that caffeine-containing “energy drinks” should not be consumed by children and adolescents.¹⁰

Macronutrient Use for Athletic Performance—Basic Concepts

Macronutrients (carbohydrates, fats, proteins) play pivotal roles in athletic performance and muscle development, but each type of macronutrient has unique properties and use. Even during competition, the primary drive is to preserve muscle glycogen for “fight or flight” responses. Four primary concepts explain sports nutrition macronutrient intake and its contribution to energy provision for athletic performance. First, when the athlete is not exercising, unused energy from ingested macronutrients are stored for later use. If muscle glycogen stores are full, the remainder is converted to and stored as fat. Second, during exercise, stored macronutrients are used slowly according to the exerciser’s aerobic capacity to burn fats rather than glycogen, thus preserving glycogen. The oxidation of fatty acids is the primary mode of energy release and consumption for aerobically intense activity. Third, muscle glycogen is depleted slowly at lower intensities or when the athlete is aerobically adapted to use fats. By comparison, muscle glycogen is depleted rapidly at high intensities, particularly when the athlete is trained to use carbohydrates as fuel or expects carbohydrate availability during the event. Finally, at the highest intensities, an anaerobic energy system contributes energy from muscle phosphocreatine (i.e., creatine phosphate) directly to depleted adenosine diphosphate (ADP), permitting restoration of muscle adenosine triphosphate (ATP).

The first concept of energy use in exercise is that of glycogen preservation and preferential fatty acid oxidation in aerobic environments. Humans are biologically designed to maintain a full reserve of glycogen as an immediate energy source for short-duration, high-intensity activity, such as fight or flight. At the lowest level of exercise intensity, a walking state, calorie utilization per minute is minimal, with 80% of the calories obtained from fatty acid oxidation and the remaining 20% derived from carbohydrates.^{11,12} As exercise intensity

increases on progression from walking to aerobic jogging, calorie consumption per minute increases, and fatty acid oxidation continues to provide about 80% of the fuel.^{11,12} Conversion of fatty acids to energy is slow and rate-limited, and the conversion rate varies for different athletes. Fatty acid oxidation is increased by low carbohydrate availability in the diet and by adaptation to aerobic physical exercise.¹³ No proposed ergogenic supplements have been shown to consistently improve the rate of fatty acid metabolism.^{1,2} A detailed discussion of fatty-acid metabolism is beyond the scope of this chapter and can be found elsewhere in the literature.^{12,13}

Second, calories burned per minute from fats are limited and reach a plateau; at that point, athletic performance will be impaired without additional calories from other sources such as carbohydrates.¹¹⁻¹³ At the intensity of a fast run, such as a 10-km race, fatty acid oxidation cannot meet all energy requirements, and energy from carbohydrate utilization is added to that derived from fats. At this level of intensity, carbohydrate utilization increases to 30% of total calorie expenditure.¹⁴ The percentage of energy from carbohydrate oxidation rises to 50% and 70%, respectively, for sprint events of 400 m and 200 m.¹⁴ Progression of exercise intensity from walking to running to sprinting is a component of many sports activities, and some sports, such as soccer and field hockey, involve a combination of extreme high-intensity effort intermixed with efforts at a more aerobic pace. The oxidation of fatty acids is the predominant mode of fuel generation until exercise intensity requires the faster energy conversion from carbohydrates.

Third, glycogen depletion is mediated by both intensity and duration of activity. Marathon runners refer to the subjective experience of muscle glycogen depletion as “hitting the wall.” A similar term, “bonking,” references the cognitive and mental attention deficits incurred when glycogen depletion leads to hypoglycemia. Limited storage capacity exists for glucose as glycogen within the liver and skeletal muscle; an average 150-pound person stores only about 2000 total calories of glycogen. High-intensity exercise over time depletes glycogen stores.^{11,12} Muscle glycogen is burned initially, and as this resource is depleted, the liver releases glucose from stored glycogen to maintain serum glucose levels. When both muscle and liver glycogen stores are depleted, serum glucose decreases and athletic performance declines. Sudden drops in blood glucose levels affect the athlete’s mental acuity, attention, and focus.^{11,12} Endurance athletes slow to an aerobic effort in which fatty acid mobilization predominates, but they are less competitive at that

level of exercise intensity. Athletes participating in sports that require high-level cognitive skills, such as shooting sports, archery, and automobile racing, experience lower performance and brain activity as their serum glucose levels decrease.^{1,2} The rate of glycogen depletion is dependent on the intensity and duration of exercise, as well as the fitness level of the athlete.^{10,11}

Endurance runners can deplete muscle glycogen in about 2–2.5 hours at a marathon run training pace; they do not require carbohydrate intake unless they exercise for that duration or longer at lower intensities (see the later section “Carbohydrate-Based Products” for recommended carbohydrate intake).^{1,2} Carbohydrate intake during the race can delay the onset of muscle glycogen depletion when running at the higher intensity of a marathon race pace. The same runners may deplete glycogen in 60 minutes when running at the faster intensity of a 10-km run, but they generally do not require carbohydrate supplements, because they complete the event in less time (30–40 minutes) than it takes to deplete muscle glycogen.^{1,2} Team sports such as football, lacrosse, field hockey, and basketball have official game time durations of 60 minutes or less, as well as time-outs, half-times, and player substitutions that allow for periods of aerobic recovery. With mandated durations for these sports, glycogen depletion is not expected to occur unless the athlete is consistently on the field playing at a high intensity. Compared with undertrained athletes, very fit athletes adapt over time to a state of efficient fatty acid utilization and require less glycogen; their carbohydrate stores are available in later stages of an event.^{11,12}

A fourth concept is that the highest intensity sports, those requiring short bursts of power lasting less than 30 seconds to 1 minute, use the phosphagen system and energy stored primarily as ATP.¹⁵ Examples are track and field events and weight lifting. Energy stored in phosphate bonds is depleted in a matter of seconds and then regenerates with rest. This energy system is discussed further in the section “Creatine.” Intermittent high-intensity sports such as football, soccer, basketball, tennis, and ice hockey use both very short (phosphagen and ATP) energy systems and intermediate (glycogen) systems over the competition range of 30–60 minutes.

Sports Nutrition Market Basics

The sports nutrition market was developed for well-trained athletes competing

at high levels of intensity and for long-duration if activity. College football players, for example, may exercise for 4 hours daily and exceed 20 hours of exercise per week. These athletes may need to provide fuel during exercise to delay or prevent glycogen depletion, or they may require rapid muscle glycogen restoration between morning and afternoon practices. Sports drinks can be consumed during practice or competition, and on-the-go fueling has replaced the concept of carbohydrate loading before long-duration events. Most marathon runners and triathletes consume carbohydrates during their events, which typically last 90–240 minutes or longer.^{1,2} Sports products also contain electrolytes to prevent deficiencies from sweat loss.

By comparison, moderate physical activity such as daily exercise for health and wellness usually occurs at a lower intensity and typically lasts 60 minutes or less per day.^{1,2} Glycogen depletion is unlikely for recreational athletes, even if they exercise 7 hours per week; consequently, carbohydrate- and electrolyte-containing sports products are unnecessary for health and wellness athletes or sedentary persons who do not participate in prolonged exercise.^{1,2}

Carbohydrate-Based Products

Carbohydrate-based sports nutrition products contain monosaccharides (e.g., glucose, fructose, galactose) as well as the disaccharide sucrose (glucose + fructose); these sugars provide rapid absorption and availability of carbohydrates. Maltodextrin (glucose + glucose as a polymer) is used in endurance formulas and is marketed as having slower absorption; maltodextrin also is tasteless, which is preferred by many athletes. Lactose (glucose + galactose), or milk sugar, also can be used as a recovery fuel after exercise.^{1,2}

The Academy guidelines for carbohydrate intake by athletes are broken down by exercise intensity and planned duration of exercise. Carbohydrate intake is not needed during exercise for events lasting less than 45 minutes regardless of intensity. For highly intense exercise lasting 45–75 minutes, the Academy considers rinsing the mouth with a sports drink during the activity as possibly performance-enhancing, although evidence for a performance benefit of this brief mouth rinse is inconsistent.^{2,16} Observations are limited to well-trained cyclists exercising for around 60 minutes and show small 1%–3% improvements in watts of energy produced, or in time trial distance covered.¹⁶ No improvements have been shown in other activities such as weight lifting or

sprinting.¹⁶ For prolonged exercise and “start and stop” sports activities that exceed 60–150 minutes, the Academy recommends intake of 30–60 g of carbohydrate per hour.¹ This recommendation translates to intake of 8–15 g of carbohydrates or 4–8 ounces of a sports drink every 15 minutes.

Most sports nutrition drinks contain 6%–8% carbohydrates for optimal absorption and gastrointestinal (GI) tolerance.^{1,2} The amount of carbohydrates is small and should be used up rapidly during continuing exercise; however, the fluid volume is relatively large. Energy gel packets are lighter and easier to carry, but they contain 20%–25% carbohydrate and should be consumed with water for dissolution. These products should be used in practice and under simulated competition to determine the athlete’s tolerance of different preparations. Research suggests that pre-exercise carbohydrate consumption may stimulate the release of insulin, potentially resulting in hypoglycemic symptoms with reduced performance in some athletes, whereas this practice has been recognized to improve performance in others.¹⁷ Ultra-endurance athletes who compete for 2.5 hours and longer may require greater than 90 g of carbohydrate intake per hour to meet energy expenditure rates even though their exercise intensity is lower.¹ The additional carbohydrate allows for longer durations (24 hours or longer) of continuous exercise. These athletes have trained to tolerate greater amounts of food during sustained exercise. Their food choices include energy-dense fats as well as protein and carbohydrate. The various carbohydrate forms (i.e., drinks, gels, bars) do not differ in their effectiveness, although individual athletes’ tolerances to various forms may differ. However, these products do vary in amounts of water and electrolytes and specific sugar sources. Bars and gels are lighter and easier to carry than an equivalent amount of calories in the form of a sports drink; however, bars and gels require a water source for proper dissolution, absorption, and GI tolerance. In addition, compared with sports drinks, the bars tend to contain other macronutrients, such as fats, proteins, and vitamins, making them better suited for lower intensity exercise or exercise that does not involve as much jostling, such as cycling. Bars also are convenient for recovery after exercise.

Although the original intent of these products was to provide fuel on the go, the market has evolved to provide meal replacements for active people in a hurry. These products are misunderstood by the public as healthier than soft drinks, candy bars, or even regular meals, despite their high sugar and caloric content. Health care providers should be prepared to read and interpret the

nutrition label with patients and to calculate total calories if the package offers multiple servings. These products are not required by active adults or children who exercise 60–90 minutes in any one session.^{1,10} Recreational athletes and sedentary persons should be discouraged from using these products before, during, or after exercise that lasts less than 90 minutes.^{1,10} The Academy and AAP recommend eating a meal after exercise as a suitable glycogen recovery method.^{1,10} Examples of bars, gels, and drinks are presented in [Table 25–1](#).

Table 25–1 Sports Nutrition Products^a

Product	Serving Size	Energy (kcal)	Carbohydrate (g)	Sugar (g)	Protein (g)	Fat (g)	Sodium (mg)	Potassium (mg)
Electrolyte Drinks and Wafers (low calorie)^b								
Gatorade Zero	12 ounces	0	0	0	0	0	160	45
Gatorade G2 Low Cal	12 ounces	30	8	8	0	0	160	45
Nuun Active Tablet	16 ounces, 1 wafer	10	1	1	0	0	360	100
Powerade Zero	12 ounces	0	0	0	0	0	150	35
Propel Flavored Water	20 ounces	10	2	2	0	0	270	70
Zym Endurance Tablet	16 ounces, 1 wafer	8	0	0	0	0	300	100
Energy Drinks (carbohydrates, electrolytes)^c								
Accelerade	31 g	120	19–21	19–20	5	0.5	220	90–95
	1 scoop, 12 ounces water							
Gatorade	12	85	21–22	21	0	0	164	46

Product	Serving Size	Energy (kcal)	Carbohydrate (g)	Sugar (g)	Protein (g)	Fat (g)	Sodium (mg)	Potassium (mg)
Thirst Quencher	ounces							
	20 ounces	140	35–36	34	0	0	270	75
Gatorade Endurance	12 ounces	90	22	13	0	0	310	140
Powerade	12 ounces	80	22–21	21–20	0	0	150	35
Recovery Drinks (carbohydrates, proteins, electrolytes, hydration)^d								
Endurox R4	74 g	270	52	39	13	1.5	220	180
	2 scoops, 12 ounces water							
IsoPure ZeroCarb	20 ounces	160	0	0	40	0	10–80	45–60
Milk, Low Fat, Chocolate Flavor	½ pint	140	25	24	7	1	190	382
	236 mL							
Muscle Milk, Chocolate Flavor	11 ounces	160	7	4	25	1	250	770
Energy Gels (carbohydrates, electrolytes)^e								
Accel Gel	1 packet	100	20	13	5	0	100–115	No data
Clif Shot (Chocolate)	1 packet	110	22	12	0	0	60	80
Gu (Vanilla)	1 packet	100	22	7	0	0	60	40

Product	Serving Size	Energy (kcal)	Carbohydrate (g)	Sugar (g)	Protein (g)	Fat (g)	Sodium (mg)	Potassium (mg)
Hammer Gel (Vanilla)	1 packet	90	22	2	0	0	25	12
Energy/Recovery Bars (carbohydrates, proteins, fats, electrolytes)^f								
Balance Bar Original (Chocolate Craze)	1 bar	200	21	18	14	7	160	250
Cliff Bar (Chocolate Chunk)	1 bar	250	45	22	9	5	300	210
Power Bar (Chocolate)	1 bar	230	44	26	10	4	200	140

^a Composition per serving. In a brand name product that is available in different flavors and formulations, the quantity of nutrients differs slightly among the product line extensions. (See product nutrition label or the manufacturer's website for the most current information.)

^b Intended as a healthy, low-calorie alternative to carbohydrate sports drinks. For rehydration and electrolyte replacement after exercise lasting 1 hour or less when glycogen depletion is not a concern. Performance benefits are unproved.

^c Intended for use during exercise to provide carbohydrates for energy and glycogen sparing, as well as electrolytes and water for rehydration.

^d Intended for use after exercise of prolonged duration when glycogen depletion is expected.

^e Intended for use during exercise to provide electrolytes as well as carbohydrates for energy and glycogen sparing. Require a water source for proper dissolution and absorption. Not intended for rehydration.

^f Intended for post-exercise recovery after exercise of prolonged duration when glycogen depletion is expected. Can serve as a meal replacement product. Often contain added vitamins and minerals.

Fats: Triglyceride-Containing Products

Fats are an important source of energy, fat-soluble vitamins, and essential fatty acids for athletes, and their consumption should not be severely restricted.¹ Many athletes minimize fat consumption, because they are calorie dense, and because they seek weight loss as a performance benefit. This benefit needs to be balanced with the risk of vitamin deficiency and the alteration of physiologic functions such as menstruation and pregnancy in female athletes.¹ The timing of fat intake prior to exercise is very important.¹ Long-chain triglycerides, found in typical fats and oils, should be avoided in sports nutrition products that will be used 1–2 hours before and during exercise, because they tend to slow gastric emptying and may cause discomfort, bloating, and GI intolerance during intense exercise. Medium-chain triglycerides (MCTs) are packaged into sports drinks and powders to provide an alternative fuel to glucose and to reduce muscle glycogen utilization.¹³ The moderate length (8–12 carbons) of MCTs results in absorption from the GI tract directly into the bloodstream, allowing more rapid utilization than with long-chain triglycerides, which are absorbed through the lymphatic system. Some MCT beverages are marketed to strength and conditioning athletes on low-carbohydrate diets. Clinical data in athletes suggest that MCTs are utilized metabolically within 30 minutes of ingestion, but evidence is lacking for improved performance or muscle glycogen sparing ([Table 25–1](#)).^{1,13}

Protein Products for Muscle Mass Gain

Athletes and those who exercise according to health standard recommendations may train with weights or their own body weight to maintain or build muscle. This approach allows the exerciser to perform their sport, improve performance, and prevent chronic disease such as sarcopenia and osteoporosis. Many athletes believe they need to consume large quantities of protein to provide substrates for muscle development. Dietary sources of protein include meat and dairy; vegetarian sources such as legumes, beans, and nuts; and prepackaged protein sources, such as protein powders, amino acid supplements, and various protein-containing bars, gels, and drinks.

Many variables affect nutrient requirements; in general, however, compared with less active persons, athletes who exercise for 10 or more hours per week have increased protein and calorie requirements.¹⁸ The Academy guidelines recommend protein intake of 1.2–2.0 g/kg daily in highly active adults who

participate in endurance exercise and in those who are attempting to increase body mass; this recommendation is in addition to an increased overall caloric intake to meet higher metabolic demands.¹ The Academy no longer offers a specific daily target for kilocalories per kilogram (kcal/kg) but rather uses a complicated formula to calculate an individual athlete's energy availability, whereby energy intake and energy expenditure are balanced with specific goals for body image and energy training. Determination of planned exercise expenditure will allow proper balance with energy intake, thereby avoiding ingestion of too many calories and risking unintentional weight gain.¹ (A review of the Academy guidelines is recommended for readers who seek more detailed understanding of this topic.¹) By comparison, the ISSN guidelines recommend 25 kcal/kg daily for sedentary persons and 25–35 kcal/kg daily for more casual athletes who choose a moderate exercise duration of 90–120 minutes weekly.² Competitive athletes training 15–30 hours per week may expend 600–1200 kcal per hour of intense exercise. Meeting these increased energy needs may require up to 40–70 kcal/kg daily.^{1,2} Athletes competing at this level should be referred to a clinical dietitian with a subspecialty in sports nutrition.^{1,2}

Athletes attempting to gain muscle mass may require an increased total calorie intake to balance their increased energy needs with exercise and to provide protein for muscle building.¹ For those who wish to build muscle, an important consideration is not to exceed reasonable total calorie goals, because energy intake that exceeds energy expenditure may lead to an accumulation of body fat, defeating the intent of training for a leaner body. In anecdotal reports, ingestion of 2.0–2.5 g/kg daily of protein has been described, although data supporting the effectiveness of such high intake are lacking.^{1,18,19} The marketplace offers a large number of protein supplements that provide specific protein sources, namely essential amino acids or branched-chain amino acids (BCAAs). ISSN and Academy guidelines indicate that simple adjustments to the athlete's diet can provide sufficient protein to meet dietary intake goals for increasing muscle mass.^{1,2,18} The available evidence is insufficient to support packaged protein supplements or specific amino acid mixtures as more effective for increasing body mass than eating whole foods that contain equivalent amounts of high-quality protein.^{1,2,18} The Academy recognizes, however, that the use of protein supplements may be reasonable for their convenience.²

Clinical Evidence of Protein Needs for Muscle Building

Muscle protein is in a constant state of synthesis and breakdown. Resistance exercise induces changes in muscle that effectively stimulate muscle remodeling and growth, provided that the diet offers an adequate quality of protein, with appropriate timing of intake, for that growth.¹⁸ The process is slow and requires repeated exercise stimulus, optimal nutrition, and several months to produce weight gain. Protein intake recommendations from the Academy and ISSN are similar at 1.2–2.0 and 1.4–2.0 g/kg daily, respectively.^{1,2,18} Both guidelines recommend that this protein intake be spread throughout the day, with small amounts of protein consumed every 3–4 hours.^{1,2} Well-designed studies of protein intake at 2 g/kg daily or greater have not shown consistent increases in lean body mass in comparison with the control group and indicate only increased protein oxidation for energy.¹⁸ Both the Academy and ISSN recommend consumption of a small dose of protein within 30 minutes after exercise to optimize metabolic adaption and muscle rebuilding. The Academy recommends a post-exercise protein dose of 0.25–0.3 g/kg body weight, which translates into 15–25 g of protein for a person of average body size.¹ A lack of information prevents specific recommendations for athletes on the extreme ends of the weight spectrum. Yogurt, cottage cheese, and almonds are readily available foods that provide adequate protein. Both guidelines recommend that athletes consume whole protein sources, because these will contain an appropriate amount of both essential and non-essential amino acids.^{1,2} Limited data suggest that BCAAs, particularly leucine, should be included in the protein source. Supplements and protein powders, particularly whey-based proteins, constitute a reasonable alternative to meet this need.^{1,2,18} Protein derived from rice and insect sources may prove beneficial as well, but data on these emerging markets are limited.²

Adverse Effects of Protein Supplement Use and High Protein Intake

The Academy and ISSN have concluded that protein intake up to 2.0 g/kg daily is effective and safe in healthy exercising adults.^{1,2,18} These agencies have similarly concluded that insufficient evidence is available to support the claim that high-protein diets, defined as exceeding 2.0 g/kg daily, are unsafe in the same healthy population.^{1,2,18,19} Concerns over kidney damage and bone osteoporosis have been raised but remain unproved.¹⁹ Minor adverse effects,

such as GI distress and diarrhea, have been reported. GI distress may be related to the osmolality of the final product as mixed by the user or to individual athlete tolerance to the product. More concerning are case reports of hypertension, abdominal pain, hepatitis, and renal insufficiency in military servicemen who reported using protein supplements, although the origin, quantity, and duration of protein use are not specified and testing for misbranding of the supplements was not performed.²⁰ The quantity of protein supplement contents, compared with the product label ingredients, is regularly tested and reported on websites such as that of [ConsumerLab.com](https://www.ConsumerLab.com), although no testing program validates all lot numbers. The most recent tests of protein powders found that the quantity of protein present was consistent with the label value but did find variations between test and label values for sodium and cholesterol content for a few products.²¹

Water and Electrolytes

Water and electrolytes are essential to performance. The Academy and ISSN recommend that athletes monitor their water balance and attempt to avoid dehydration, defined as a 2% decrease in total body weight, which has been shown to affect physical and mental performance.^{1,2,22} Dehydration is not just the loss of body water and corresponding body weight. Physical exercise during dehydration has multiple adverse effects, including an increase in electrolyte loss, impaired evaporative heat loss, and increased peripheral vasodilation, all of which contribute to cardiac effort and physical strain. Physical effects can be measured by elevations in core body temperature, heart rate, and perceived exertion. The greater the body water deficit, the greater the strain for a given task. Dehydration also can affect cognitive performance, such as mental concentration and focus on skilled tasks. Of note, however, an even greater degree of dehydration (with loss of 3%–5% of body weight) does not appear to affect anaerobic performance and muscle strength.²² Readers are referred to the position statement of the American College of Sports Medicine for guidelines and detailed discussion of this topic.²²

Dehydration involves water loss and electrolyte concentrations as separate issues. Athletes generate heat from exercise-related muscle contractions in proportion to the intensity and duration of exercise. This heat generation is transferred to the blood and then to the body core. Blood circulation through peripheral blood vessels and the skin allows radiant heat exchange with the

environment. Sweating, albeit with a variable degree of fluid and electrolyte loss, facilitates evaporative cooling at the skin surface. Environmental conditions such as temperature, humidity, air motion, helmets, and layers of clothing influence the success of evaporative cooling. If sweat-related water and electrolyte losses are not replaced, the athlete experiences dehydration.

The significance of dehydration depends on environmental conditions, exercise intensity, and duration of the activity. For example, compared with a recreational runner, an elite marathon runner may demonstrate a higher sweat rate, as measured by sweat loss in kilograms per hour, but both athletes will have similar total sweat losses owing to the prolonged time that the recreational athlete needs to complete the event. By comparison, when practicing under identical conditions, American football players have significantly greater sweat rates than those of soccer players.²² A higher sweat rate may be related to the layers of clothing and use of helmets, which contribute to greater heat accumulation and increased sweat and electrolyte losses, while preventing evaporative cooling.²² The risk of dehydration in any sport is further influenced by participation in twice-daily practice sessions, which may not allow adequate time between sessions for water and electrolyte replacement.¹

Health Conditions Related to Hydration and Electrolytes

Hydration can affect health status through water loss or water gain (overdrinking) and can alter serum sodium levels sufficiently to endanger health. In general, dehydration is more common, but overhydration resulting in hyponatremia can be equally life-threatening. Signs of dehydration include fatigue, confusion, irritability, and increased risk of heat illness, with symptoms of muscle cramps, heat exhaustion, heat stroke, and exertional rhabdomyolysis.²² Rhabdomyolysis has been reported as a result of dehydration, heat stress, and novel training. *Novel training* involves the introduction of new exercise patterns in athletes who have not been acclimated to such activity, such as with military recruits at boot camp or high school students attending preseason football camps.

Prevention of Dehydration

Meal consumption is an important aspect of maintaining optimal hydration status between exercise sessions.^{1,22} Eating promotes fluid intake and

retention of water, provided the meal is a sufficient source of sodium.²² Water alone is sufficient for rehydration during events lasting 60 minutes or less.^{1,10} Sports drinks can provide water and electrolytes after exercise, but on assessment the morning following a workout of 60 minutes or less, the drinks have not proved superior to a meal with water consumed after exercise.^{1,2,22}

Hyponatremia Risk From Drinking Excessive Free Water

Most laboratory-based studies of dehydration have occurred on stationary treadmills in climate-controlled rooms with little to no convective airflow to help sweat evaporation.²² On the basis of such studies, athletes have been taught to drink as much water as possible to prevent dehydration. However, liberal water intake has been called into question, particularly for endurance athletes, following clinical observations of weight gain, severe hyponatremia, cerebral edema, and death in athletes who consumed water without added electrolytes during athletic events lasting longer than 4 hours.²²⁻²⁴ Improved water availability to athletes competing in marathons has not resulted in a lower rate for seeking post-race medical care.^{23,24} The original research was directed at elite-level athletes competing for 60–150 minutes who consumed small sips of water while running very fast and generating significant body heat with high sweat rates. Unfortunately, this description does not apply to average athletes, who complete the same marathon races at a much slower pace, generate less heat accumulation, and have lower sweat rates.

Observations from actual marathon race conditions resulted in an advisory statement from the International Marathon Medical Directors Association (IMMDA).²⁴ Heat production by athletes is significantly affected by the effort expended (the combination of duration and intensity or speed of the exercise); a 10-km race effort will therefore generate more heat than a marathon effort (42.2 km). Average athletes run more slowly than elite athletes, so they are at lower risk for heat illness and have more time to consume water offered at aid stations. The result is that clinical hyponatremia occurs more frequently in nonelite athletes, particularly women, who typically require more than 4 hours to finish a marathon, and in long-course triathletes, who require 13–17 hours to complete their events.²²⁻²⁵ IMMDA recommends that fluid consumption during a race be based on the trigger of actual thirst, rather than on a set volume of fluid intake. As subjective thirst increases, the athlete can increase fluid intake from sips of water to match the previously calculated sweat rate. IMMDA strongly recommends that the athlete choose an electrolyte

replacement drink instead of free water, however, to avoid the risk of hyponatremia when competing in events that last 4 hours or longer.²⁴

Athletes competing for 2 or more hours can calculate their individual sweat rates by determining their total body weight before and after prolonged exercise. For example, an athlete who takes a 2-hour run on a hot afternoon may drop 2 kg of body weight, demonstrating a sweat rate of 1 kg per hour. Each 1-kg change in body weight is associated with a 1000-mL water deficit, so in this example, the athlete's decrease in body weight translates to a loss of 2000 mL of body water. The athlete can therefore target a drinking rate of 1000 mL per hour, or 240 mL (8 ounces) every 15 minutes, during prolonged exercise.

Appropriate athlete education before the event and provision of electrolyte-containing sports drinks during the event has resulted in a reduction in the occurrence of hyponatremia in triathletes²⁵ but not in experienced marathon runners.²²⁻²⁴ Other potential contributing factors include environmental conditions and duration of competition, as well as pharmacokinetic effects. For example, clinical observations indicate that exercise-induced hyponatremia may be more frequent with concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs) in marathon runners²³ and long-course triathletes.²⁵ An exact mechanism is unknown; however, NSAIDs may interfere with normal prostaglandin-mediated regulation of glomerular filtration and renal blood flow. Triathletes with significant hyponatremia have been observed to have elevated nitrogen and potassium levels, suggestive of reduced glomerular filtration.²⁵

Postural hypotension, rather than heat-related illness or dehydration, has been recognized as a health risk in endurance running that is not directly related to fluid intake. When a runner crosses the finish line and then stops, the sudden cessation of leg muscle contractions allows pooling of blood in the lower limbs, with consequent decreased venous return. The resulting drop in cardiac output may leave the brain under perfused with oxygenated blood, causing the affected athlete to black out.²⁴ To prevent this reaction, the athlete should continue walking past the finish line.

Only athletes demonstrating a rectal temperature higher than 104°F (40°C) should be treated for heat illness.²⁴

Carbonated and Oxygen-Enhanced Water

Available research does not substantiate a performance benefit of oxygenated water or carbonated water in humans.^{22,26} Dissolved gases from consumption of such products can accumulate, with consequent GI distress and bloating, resulting in decreased total fluid consumption.²² According to purveyors of oxygenated water, it contains 30% or higher dissolved oxygen; when marketed in plastic bottles, however, it may contain no more dissolved oxygen than tap water, and 12 ounces of oxygenated water in glass bottles contains less oxygen than that in a single breath of room air.²⁶

Electrolytes and Water Without Added Carbohydrates

Several carbohydrate-free products that offer water, electrolytes, and vitamins have been developed; they contain an artificial sweetener to replace most or all carbohydrates typically found in a carbohydrate-containing sports drink. Low-calorie carbohydrate-containing sports drinks provide as little as 3–8 g of carbohydrates per 8-ounce serving, or just 12–32 kcal, contrasting with 11–18 g of carbohydrates and 44–72 kcal per 8-ounce serving of most carbohydrate-containing sports drinks. These low-calorie and no-calorie electrolyte waters have not been evaluated for performance benefits. An alternative to carbohydrate-containing sports drinks is artificially sweetened electrolyte drinks, but they offer no more performance benefits than water does, other than the observation that a small amount of added sweetness to offset the sodium may encourage consumption of a greater volume of fluid.^{1,22}

Electrolytes, Carbohydrates, and Water

Addition of carbohydrates to sports drinks benefits athletes competing longer than 60–90 minutes by replacing muscle glycogen lost during periods of intense or prolonged effort. Carbohydrate supplementation during exercise provides exercising muscles with fuel for energy while allowing muscles to conserve stored carbohydrate energy as glycogen. This strategy of providing fuel during exercise at a rate of 30–60 g per hour for events lasting longer than 60 minutes has been shown to prolong the time to exhaustion in football and soccer players, as well as in long-distance endurance athletes such as runners and cyclists.¹ Carbohydrate-containing sports drinks appropriate for consumption during exercise provide 6%–7% carbohydrate concentration. To meet the target of 30–60 g of carbohydrate per hour, the athlete would drink

500–1000 mL per hour. Many triathletes and runners use a combination of carbohydrate-containing drinks and gels or chews, which must be consumed with water or another fluid to assist in dissolution and absorption of the carbohydrate.

Electrolytes, Carbohydrates, Protein, and Water

Several sports nutrition drinks combine an electrolyte– carbohydrate solution with added protein. The protein provides an additional metabolic fuel for ATP production.^{27,28} These products are marketed to endurance athletes competing at aerobic intensities for long-duration events, including marathon runners (2.5–5 hours), long-distance triathletes (2–17 hours), and adventure racers (12 hours to 5 days). Only a few studies have compared carbohydrate-only with carbohydrate plus added protein products. The studies that carefully controlled for equal caloric consumption between two groups of subjects have consistently demonstrated equivalent performance effects on cycling exercise duration.^{27,28} However, the group of subjects who drank the carbohydrate–protein solution showed significantly lower creatine kinase levels and perceived less muscle soreness on the day after the exercise. Unfortunately, these studies did not measure cycling performance on subsequent days and cannot be used to show an association between the observed muscle soreness and its effect on future exercise performance.^{27,28}

Although ready-to-drink options are available, some protein-containing drinks are powders that require reconstitution and can release significant amounts of gas when mixed with water. Bubbles and foam appear in the hydrated powder, which can influence GI tolerance in athletes. Protein-containing sports drinks should be introduced during the training regimen so that athletes can determine their tolerance to the products and the products' impact on performance before using such drinks during an event. Of note, because hydrolysis can affect stability of some proteins once they are mixed with water, protein-containing dry-powder drinks should never be prepared the night before an event. Optimal protein potency and effect may require athletes to carry unmixed powder and add water during the race, a potentially unsafe practice. For example, a triathlon participant attempting to prepare such a drink could lose control during the bicycling portion of the event. Once mixed, all sports drinks should be consumed or stored in the refrigerator within 2 hours to prevent bacterial growth.

Pre-exercise Nutrition and Hydration

The Academy guidelines recommend that a hydration fluid of 5–10 mL/kg of body weight be consumed 2–4 hours before exercise.¹ As an example, for a 59-kg athlete, appropriate early hydration would consist of 295–590 mL of fluid. This timing allows for the excretion of excess fluid in the urine before exercise begins. Hyperhydration with glycerol increases the risk of needing to void during competition, provides minimal performance advantage, and is discouraged.^{22,29}

The timing of pre-exercise carbohydrates is controversial. Eating a meal before exercising or competition can affect the athlete's performance through GI intolerance and the body's metabolic response to nutrient intake. Athletes are encouraged to allow several hours between a meal and exercise to allow for digestion and absorption of foods consumed, as well as to permit stabilization of metabolic responses such as insulin release and serum glucose levels before exercise.^{30,31} Carbohydrate intake before exercise is intended to ensure optimal muscle glycogen for competition. However, studies of pre-exercise carbohydrate intake in the 60 minutes before exercise have shown varied effects on performance.^{30,31} A carbohydrate load is known to stimulate insulin release, which has been measured after pre-exercise doses of 25–125 g.³¹ The release of insulin signals carbohydrate availability beyond what is needed for immediate use, and thus insulin signals for carbohydrate storage. When carbohydrates are abundant, fatty acid oxidation is not needed, and we see that insulin inhibits the release of the enzyme lipoprotein lipase.

Lipoprotein lipase is responsible for the hydrolysis of a triglyceride molecule into free fatty acids, and one glycerol molecule.^{11,13} Cellular uptake of the free fatty acids for oxidation is increased in the presence of lipoprotein lipase, and inhibited by the presence of insulin.^{11,13} The effect of insulin on the inhibition of lipoprotein lipase is evidenced by the dramatic drop in serum glycerol following a carbohydrate load.³¹ The metabolic result of the pre-exercise glucose load is that the athlete is inhibited from the efficient use fatty acid oxidation for energy and becomes more dependent on carbohydrate energy sources.

Introducing exercise after these metabolic changes is associated with serum glucose depletion and observations of hypoglycemia in as little as 15 minutes of exercise at moderate to high intensity (>70% of maximal oxygen

consumption—i.e., $\text{Vo}_{2\text{max}}$).³¹ Observational studies of hypoglycemia risk in the laboratory have been highly variable and inconclusive in that not all athlete's experience a clinical hypoglycemia.^{13,31}

The performance impact of pre-exercise nutrition is affected by many variables, such as the type, intensity, and duration of activity and the availability of additional carbohydrate during exercise. What is known is that the athlete will disproportionately use serum glucose for energy, because the insulin effect inhibits glycogen breakdown from the liver and dramatically reduces the energy provision from fatty acid oxidation. American football and soccer athletes who train with carbohydrate loading and continued carbohydrate maintenance doses during sustained exercise are essentially unaffected. By comparison, a long-distance runner who trains in a fasted state has adapted to aerobic fatty acid oxidation as a primary means of fuel generation. The long-distance runner is more likely to experience an unintended reduction in performance on introducing a carbohydrate load immediately (<60 minutes) before a prolonged running event.

The Academy guidelines state that optimal performance depends on individually determined distribution of macronutrient intake before exercise, because of variations in athlete body habitus, the energy demands of different sports, overall daily calorie needs, and the timing of macronutrient intake before the practice or event. Individual athletes should consider nutrition a part of their training regimen, with attention to timing, quality, and quantity of intake for establishing their own tolerance and timing.

Nutrition and Hydration During Exercise

As detailed previously, for competitions lasting longer than 60–90 minutes, athletes are recommended to determine a sweat rate by measuring pre- and post-exercise body weights. A reasonable goal is to drink 16–24 fluid ounces of a sports drink for every 0.5 kg of body weight lost during exercise.¹ Similarly, the Academy recommends carbohydrate provision during exercise lasting longer than 60–90 minutes as a method to preserve muscle glycogen. The Academy guideline recommends consuming 30–60 g of carbohydrate (from food and/or fluids) per hour during exercise to maintain blood glucose levels.² A carbohydrate drink concentration of 6%–8% is recommended, because concentrations greater than 8% are associated with adverse GI effects.¹ Athletes who intend to consume carbohydrates in the 60 minutes prior to

exercise or during prolonged exercise should train with carbohydrate provision, to assess their individual exercise tolerance to these carbohydrates.

Post-exercise Nutrition and Recovery Drinks

Goals of post-exercise recovery nutrition are to rehydrate, to restore muscle glycogen, and to provide protein to repair muscle damage and synthesize new muscle tissue, thereby preparing the athlete for another period of activity. The choice of recovery nutrition depends on how much time is available until the next session of intense activity. When the athlete's recovery time between bouts of exercise will be 4 hours or longer, the Academy recommends consumption of a balanced meal or snack after exercise for glycogen restoration, optimal rehydration, and correction of electrolyte imbalances.¹ No benefits are recognized for consumption of sports nutrition products compared with eating a meal in this setting.

Several studies have compared a carbohydrate-only sports drink with consuming low-fat milk containing an equal number of calories from low concentrations of fat, carbohydrate, and protein.³²⁻³⁴ Consumption of low-fat milk was associated with a greater degree of rehydration, lower urine output, and improved body weight recovery when measured 4 hours after dehydration-inducing exercise.³² In addition, low-fat milk was associated with a longer time to exhaustion in subsequent exercise sessions.^{33,34} Milk is an effective after-exercise option and is better for recovery than a carbohydrate-only sports drink. Of note, low-fat and skim milk should not be confused with products such as Muscle Milk, which is advertised as a nondairy product despite containing milk protein isolate, and calcium and sodium caseinates from milk. Compared with low-fat or skim milk, each serving of Muscle Milk contains considerably more calories in the form of added fats and high-glycemic-index carbohydrate.

When recovery time will be less than 4 hours, drinking a carbohydrate sports drink improves muscle glycogen recovery better than drinking water. The sooner the carbohydrate is consumed after exercise, the sooner muscle glycogen is replaced. The Academy guidelines recommend carbohydrate consumption of 1.0–1.2 g/kg per hour for the first 4 hours after a glycogen-depleting exercise.¹

Safety and Efficacy of Specific Ergogenic Supplements

This section discusses evidence that supports the safety and efficacy of specific nutritional supplements and micronutrients for sports performance—namely, herbs, plant extracts, antioxidants, and other supplements purported to improve sports performance. These nutritional supplements are marketed as “foods” and are not regulated as drugs by FDA. Accordingly, manufacturers of such foods are not required to provide safety and efficacy data in humans to prove their effectiveness on the playing field, nor is testing required to prove the labeled content of such foods. As noted previously, abundant evidence has accrued for misbranding and the frequent inclusion of substances banned by antidoping agencies in these products.^{4–6} **Table 25–2**^{1,2,35–45} lists substances for which available evidence does not support claimed effectiveness. Athletes should be reminded that extreme caution is warranted with use of nutritional supplements to enhance sports performance: Misbranding of these supplements may lead to doping infractions, and serious adverse effects and deaths have been reported from supplement use.

Table 25–2 Selected Products Marketed as Ergogenic Supplements

Ingredient	Marketed Claim	Conclusion/Evidence
Antioxidants ^{1,2,35}	Claims for antioxidants include ability to reduce oxidative stress from exercise and/or to speed recovery after exercise. Many antioxidants have been included in sports nutrition supplements, including alpha-lipoic acid, carotenoids, glutathione, <i>N</i> -acetylcysteine, ubiquinones (coenzyme Q10), vitamin B complex, vitamin C, and vitamin E.	Evidence does not support an effect on reducing oxidative damage or enhancing performance. Frequent exercise is associated with an enhanced antioxidant system.
Arginine ²	Arginine has been promoted to improve muscle building and cardiovascular functioning through the production of nitrous oxide, which causes cardiac vasodilation and increased oxygen delivery to the heart.	Evidence does not support an effect on performance enhancement.
Branched-chain amino acids	BCAAs are isoleucine, leucine, and valine. Skeletal muscle cells use BCAAs to supply energy during	Evidence does not consistently support an

Ingredient	Marketed Claim	Conclusion/Evidence
(BCAAs) ^{1,2}	exercise. Supplementation may reduce fatigue and increase exercise time to exhaustion by reducing serum levels of L-tryptophan and its effect on serotonin levels in the brain.	effect on endurance performance.
Beta-alanine ³⁶	Beta-alanine supplementation improves muscle carnosine concentrations. Work capacity may improve in short efforts (<120 seconds) but not in longer efforts.	The primary literature does not consistently support an effect on performance.
Carnitine ²	Carnitine is an essential cofactor for the transport of long-chain fatty acids into the mitochondria. Product is proposed to improve fatty acid oxidation, fat burning, and oxygen absorption as well as to reduce lactic acid accumulation.	Evidence does not support an effect on performance.
Chromium ²	Chromium is marketed to enhance carbohydrate utilization in the body, promoting fat burning and dietary protein sparing for muscle building.	Evidence does not support an effect on performance.
Citrulline ²	L-Citrulline is a metabolic precursor to arginine. Citrulline is not affected by first-pass hepatic metabolism and is converted by the kidneys to arginine. Product is proposed to improve oxygen consumption and time to exhaustion in treadmill running.	Evidence does not support an effect on performance.
Conjugated linoleic acid (CLA) ²	CLA is promoted to endurance athletes as a thermogenic aid, body fat reducer, and ergogenic aid that enhances fat metabolism. CLA may increase cardiac risk by lowering high-density lipoprotein and increasing lipoprotein(a) concentrations.	Evidence does not support an effect on performance or body composition.
<i>Cordyceps sinensis</i> ³⁷⁻³⁹	<i>Cordyceps sinensis</i> is used in Chinese medicine to treat lung disease and fatigue. Products claim that this mushroom can decrease oxygen consumption and improve endurance. Product is frequently combined with <i>Rhodiola</i> .	Evidence does not consistently support an effect on performance.
Eleuthero ⁴⁰	Extracts of Siberian ginseng have been reported to affect cardiorespiratory performance, fat metabolism, and improved endurance.	Evidence does not support an effect on performance.
Ginseng ⁴¹	Extracts of <i>Panax ginseng</i> have been reported to improve lactate clearance and delay the onset of	Evidence does not support an effect on

Ingredient	Marketed Claim	Conclusion/Evidence
	fatigue.	performance.
Glycerol ^{1,42}	Glycerol is reported to act as an osmotic agent to promote hyperhydration before exercise, thereby reducing the risk of dehydration from intensive exercise in the heat.	Evidence does not support an effect on performance.
Hydroxy-methylbutyrate (HMB) ^{1,2,43}	Beta-HMB is a metabolite of leucine metabolism, purported to increase fat-free mass by reducing muscle protein breakdown after a workout and to increase protein synthesis. HMB also has been proposed to improve aerobic performance.	Evidence supports an increase in fat-free mass but does not consistently support effects on performance. Untrained subjects appear to receive greater benefit than trained athletes.
Lecithin ⁴⁴	Lecithin is a source of choline and a precursor to acetylcholine. Decreased plasma choline and acetylcholine levels have been reported in marathon runners. Supplementation of lecithin before a marathon does prevent the decline in serum acetylcholine levels but does not affect finishing times.	Evidence does not support an effect on performance.
<i>Rhodiola</i> sp. ^{37-39,45}	<i>Rhodiola rosea</i> and <i>Rhodiola crenulata</i> are Chinese herbs used to stimulate the nervous system, improve aerobic work performance, and reduce fatigue. <i>Rhodiola</i> is reported to improve oxygenation at high altitudes and to elevate the lactate threshold. Endurance athletes have seen 1%-2% reductions in cycling time trials and running events.	Evidence suggests small improvements in endurance exercise that are minimal enough to question the herbs' performance value.

Caffeine and Caffeine-Supplemented Energy Drinks

Caffeine supplementation has shown effects in some, but not all, anaerobic resistance exercises (weight lifting).^{2,46} Pre-exercise caffeine doses of 2 mg/kg have improved duration of endurance exercise but not measured oxygen uptake.⁴⁶ Caffeine has no effect on high-intensity sprints or on agility tests.^{2,46} It does improve alertness in very-long-duration endurance races, such as 24-hour bicycle races, because it may counteract sleep deprivation. Caffeine

doses affecting sports performance (2–6 mg/kg) are similar to doses that can be obtained from foods and beverages that are unrelated to exercise or performance. Doses exceeding 9 mg/kg do not add benefit.⁴⁶ Incidental exposure to caffeine is common, and complete avoidance is unrealistic. WADA does not list caffeine as a problematic substance, and many questions regarding the effective use of caffeine for ergogenic benefit are still unanswered.

The class of products labeled as providing “energy” is broad and increasingly popular, although the vast majority of consumption is recreational and unrelated to sports.^{3,47} Although the composition of sports drinks is similar to that of energy drinks (EDs) and energy shots (ESs), both EDs and ESs contain caffeine in addition to water and electrolytes. EDs may contain carbohydrates or be labeled as “calorie free.” They usually contain a blend of other nutrients and herbal additives such as taurine or guarana that are proposed to affect exercise performance or mental performance during exercise. These additives have not been proved to affect sports performance or weight loss.⁴⁸

EDs are not without risk of unintended adverse effects. The additional caloric load may affect blood glucose and insulin levels and consequently promote weight gain.⁴⁸ Weight gain and increases in body mass index have been reported in sedentary children who drink EDs.⁴⁹ EDs are more acidic than sports drinks, and have been associated with a faster rate of enamel loss when teeth are exposed to both products in a controlled lab environment.⁵⁰ Users of EDs also are cautioned to consider the possible adverse effects from cumulative daily doses of caffeine. Limits on the amount of caffeine present in EDs are not enforced within the United States at this time. Caffeine content of U.S. products varies, with a reported range of 100–286 mg per serving, whereas Canada has limited EDs to 180 mg of caffeine per drink.⁴⁸ This quantity of caffeine is similar to that in a 16-ounce serving of coffee. In addition to GI intolerance, adverse effects include insomnia, nervousness, tachycardia, tremors, and anxiety. A recent clinical observation in healthy college-age adults showed that a single dose of an ES can increase systolic and diastolic blood pressure by 5 mm Hg from baseline, although none of the healthy subjects were reported to have reached a level of prehypertension.⁵¹ More severe adverse effects from EDs have been recorded for emergency department visits related to the indiscriminate use of EDs mixed with alcohol.⁵² A more recent meta-analysis, however, contradicts earlier research and concludes that users of ED mixed with alcohol are not more likely to abuse

alcohol or to engage in risky behaviors such as drinking and driving as compared with users of ED alone.⁵³

AAP has concluded that children and school-age athletes should not consume EDs or ESs and that they have no place in sports competition.⁹ ISSN further states that diabetics and persons with preexisting cardiovascular, neurologic, or metabolic disorders should avoid these products.⁴⁸ Avoiding the use of EDs and ESs for sports performance generally is appropriate advice for any age group.

Creatine

Creatine is the most widely used ergogenic aid among athletes, and it has the most consistent data.¹⁵ Creatine, a naturally occurring substance, is synthesized in the body by the combining of arginine and glycine, or it is absorbed intact after ingestion of red meat and fish.¹⁵ Creatine is found in all skeletal muscle as free creatine or high-energy phosphorylated creatine (PCr). PCr functions as an energy buffer, transferring a phosphate group to ADP, thereby rapidly regenerating ATP during periods of exercise. Skeletal muscle contains limited amounts of energy stored as ATP at rest; exercise depletes this stored ATP energy quickly. The body must oxidize macronutrients through the Krebs cycle to restore ADP to the high-energy ATP state for continuous or repeated efforts. PCr transfers its energy to ADP in seconds, acting as a secondary fuel. However, the total amount of PCr energy in muscles lasts for only 20–30 seconds.¹⁵

Performance gains with creatine are limited to laboratory-based studies of short bursts of anaerobic activity lasting 30 seconds or less. Creatine supplementation attenuates normal decreases in the force associated with repeated work applications.¹⁵ For example, a weight lifter may perform three sets of a bench press, with a goal of 10 lifts, or repetitions, per set. The lifter takes 30 seconds of rest between each set. Ordinarily, the lifter may be able to move a certain amount of weight for 10 repetitions in the first set, 8 repetitions in the second set, and only 6 repetitions in the third set. The decrease in number of possible lifts is called *attenuation* and is related to decreased energy (ATP) in the muscles. Creatine can improve the amount of ATP energy available to lift the weight, allowing the same athlete to complete more repetitions in each subsequent set (e.g., 10, 10, and 8 repetitions rather than 10, 8, and 6).¹⁵ Similar improvements in maximum weight in a single lift also have

been reported.¹⁵ Creatine is useful for athletes participating in events that require repeated, short, explosive bursts of power, such as sprinting and jumping as seen in American football, soccer, and track and field events. By comparison, creatine does not benefit athletes in sports that require more than 20–30 seconds of high-intensity activity. Thus, with aerobic activities as short as 800-m (2-minute) and 1600-m (5-minute) runs on a track, no performance benefit has been shown with use of creatine.¹⁵

Current evidence does not support that creatine can induce structural changes in muscle fibers. The muscles may be larger and weigh more, owing to the presence of creatine and water in complex with creatine. The athlete may gain mass and appear stronger in the gym, but this change is dependent on maintenance supplementation. Short-term studies show a return to normal muscle creatine concentrations and depletion of the extra PCr energy on cessation of creatine supplementation. Creatine itself does not appear to cause permanent alteration of muscle fiber types.^{54,55} Poor study design and inappropriate statistical analysis will affect interpretation of existing studies. An observation of an increased number of satellite cells after 8 weeks of supplementation was not validated when observed again after 12 weeks nor was it confirmed as permanent after cessation of supplement use.⁵⁴ Muscle satellite cells can form or repair myofibers in skeletal muscle. A similar observation of increased myosin heavy chain expression and an increase in “fast twitch” type IIx muscle fibers was not properly evaluated between groups or confirmed as a permanent change by reassessment of the muscle after cessation of use and “washout” of the supplement.⁵⁵

Loading doses of creatine are not required if performance benefits are not desired within 10–14 days.¹⁵ A maintenance dose of 5–6 g daily is adequate to boost muscle creatine levels and is associated with fewer GI adverse effects. If an immediate improvement in strength is required, benefits can be detected at 5 days after a loading dose of creatine at 20 g daily (or 0.3 g/kg daily).¹⁵ This loading dose usually is divided into 4 doses to reduce GI adverse effects of stomach upset and nausea. Nausea may be related to osmotic effects or to malabsorption. Muscle cramping has been reported, but dehydration and heat-related illness have not been associated with long-term studies of creatine supplementation.¹⁵ However, creatine supplements have been reported to be misbranded and to contain substances banned by antidoping agencies.^{4,6}

All athletes should be discouraged from using creatine supplements until regulated testing of such products is required. They should be encouraged to seek natural creatine sources from food rather than from supplements. When the athlete insists on using creatine, health care providers should emphasize that supplementation should be used only as long as necessary (e.g., only during the competitive season). No reason exists to continue the supplements during the off season. Health care providers also should recommend appropriate additional hydration during creatine exposure, because creatine is a protein that is filtered through the kidneys. For an athlete who becomes significantly dehydrated, it is best to temporarily hold creatine use until proper fluid balance is restored.

Dimethylamylamine

Dimethylamylamine (DMAA), also known as methylhexanamine, was previously marketed as a sympathomimetic to treat nasal congestion. DMAA appeared in nutritional supplements following the FDA ban on ephedra, with product labeling claims that include increased muscle mass and thermogenesis to reduce body weight. Product claims also imply that the chemical was derived from a natural source, such as geranium extract. Use of these products has been associated with multiple cases of cardiac toxicity, acute hepatic failure, liver transplantation, and death from cardiogenic shock.^{56,57} A report from the Centers for Disease Control and Prevention (CDC) noted 29 cases of hepatic failure, with 40% of affected users requiring hospitalization. In this report, 24 people had used a DMAA-containing supplement in the 60 days before onset of hepatic injury, and 12 of these denied taking any other supplement besides the DMAA-containing product.⁵⁶ Dimethylamylamine is currently banned by the FDA but may appear in supplements from outside of the United States or as a misbranded ingredient in marketed products.

Ephedra and Pseudoephedrine

Pseudoephedrine is available without a prescription, but even when it is taken temporarily for appropriate medical reasons, its use may be troublesome for elite athletes, because it may be detected in random drug testing. Urine concentrations of pseudoephedrine greater than 150 mcg/mL are flagged as prohibited use by WADA. No evidence supports performance enhancement with pseudoephedrine at nonprescription doses (120 mg daily).⁵⁸ However,

when pseudoephedrine was taken at 2.5 mg/kg, roughly 5 times the recommended nonprescription dose, one study of 7 runners showed an average 6-second improvement in 1500-m time.⁵⁹ Reports that ephedra was associated with hypertension, cardiac arrhythmias, and seizures in otherwise healthy young adults were used to determine that ephedra was unsafe for human consumption, and ephedrine alkaloids were banned from U.S. markets in 2004.⁶⁰ No data support ephedra as useful for athletic performance.⁵⁸ Athletes and consumers should be aware that plant alkaloids related to ephedra may appear in nutritional supplements (e.g., ma huang, Mormon tea, some weight loss supplements). Ephedra continues to be available in foreign markets and through internet sales.

Steroidal Precursors, Dehydroepiandrosterone, and Aromatization Inhibitors

The Anabolic Steroid Control Act of 2004 classified hormone substances that are pharmacologically related to testosterone as legend, or prescription-only, drugs. Androstenedione and prohormone precursors to testosterone were sold as nutritional supplements before passage of the Act, but more recently they have been identified as misbranded ingredients in nutritional supplements sold through the Internet. Dehydroepiandrosterone (DHEA) is a precursor to more potent androgens such as testosterone. In well-designed studies, DHEA supplementation resulted in significant elevations in estradiol and estrone, but no elevations in serum testosterone, in men who took the supplement.⁶¹ Aromatase inhibitors prevent the conversion of testosterone to estrone, and their use is specifically prohibited by the antidoping agencies. Many body-building supplements claim to include substances, such as *Tribulus terrestris*, that act as aromatase inhibitors. No data support these claims; however, some supplements have been misbranded with the legend drug tamoxifen.^{5,6} Products with claims (implied or otherwise) to boost testosterone or provide aromatase inhibition should not be recommended as performance-enhancing supplements.

Stacking Products and Use of Proprietary Blends

Sports nutrition products often combine several agents into a single product, a process known as “stacking,” with the implication that they work better together than separately. In a similar fashion, sports nutrition products provide

a blend of ingredients but label these ingredient amounts as “proprietary” to avoid having full disclosure on the label.⁶² Blended ingredients may include vitamins, minerals, metabolites, amino acids, or herbal supplements. Advertising for these ingredient blends indicates that they are added to improve muscle strength, to reduce oxidative stress, or to enhance fat metabolism. The quantity of each ingredient should be included on the label. A recent investigation of 100 sports performance products sold over the counter found that these products had an average of 8.1 ingredients with undisclosed quantities.⁶² When quantities per serving were properly labeled, it was common for ingredients such as caffeine to be present in a less-than-efficacious dose.⁶² Ingredients for which available data are insufficient to support a clear positive effect on performance are reviewed in [Table 25–2](#).^{1,2,35–45}

Assessment of Performance-Enhancing Nutrients: A Case-Based Approach

Performance enhancers run the gamut from electrolyte solutions to energy bars to herbal supplements. To help in selecting an appropriate product, the health care provider should determine the type of exercise or physical activity in which the athlete engages, the expected intensity and duration of activity, and any products previously tried. The person also should be asked about any ill effects experienced after physical activity or after using a performance enhancer.

Cases 25–1 and 25–2 illustrate basic assessment of two different athletes who wish to use a performance-enhancing product.

Sales of sports nutrition products designed to enhance or improve performance are increasing every year. The most common self-treatments are use of creatine to improve muscle power and ingestion of carbohydrates during exercise to preserve muscle glycogen and to prolong time to fatigue across all sports. Several herbal supplements claim to enhance performance, but evidence to support these claims is currently lacking. Although these natural herbal products are touted as safe, evidence suggests that some may have detrimental effects on long-term health in that they increase cardiovascular risk by reducing levels of high-density lipoprotein.

Case 25–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient is a recreational runner and father of three children who wishes to lose weight and improve his running endurance so that he can complete a marathon. He reports feeling confident through 10 miles of running, but then his pace declines around mile 9 and he is not able to sustain the 10 minutes per mile pace beyond 90 minutes. He also complains of muscle soreness for 2 days after his long runs. The muscle soreness affects his movement at work, which can be significant during 12-hour shifts.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Mr. Platt started running again 6 months ago and has completed several 10k races. Initially, he could barely run for 20 minutes at a pace of 12 minutes/mile, primarily owing to deconditioning and weight gain. His initial weight and BMI were 86 kg and 27.8 kg/m ² , respectively. He has seen his endurance and pace improve with training and a loss of 5 kg total body weight. He has reached a plateau of endurance, with performance declines starting around 60–70 minutes into his runs. The fatigue he experiences also is less common on cool morning runs and is more significant on warm humid days, when he sweats more.
c. Description of the patient's efforts to relieve the symptoms	The patient believes that weight loss is needed, because he ran half-marathons at a pace of 8 minutes per mile when he served in the Army 5 years previously. His weight and BMI were 74 kg and 24.1 kg/m ² at his discharge, and he associates his weight with his performance. He has avoided the sports nutrition products used by his training partners, considering them to be calorie-dense. However, he knows to avoid hyponatremia and adds a dash of salt to his water bottle. He currently drinks less than 120 mL of water per hour. He has taken his bathroom scale to the park where he trains. In his last 120-minute run, he measured a

	3-pound (1.6-kg) weight loss.
d. Patient's identity	Paul Platt
e. Patient's age, gender, height, and weight	37 years, male, 5 ft 9 in., 178 lb (81 kg)
f. Patient's occupation	Critical care ICU nurse
g. Patient's dietary habits	Mr. Platt works 12-hour shifts in the surgical ICU of a teaching hospital. He has been making poor decisions on food selection from the cafeteria, which serves hamburgers, hot dogs, and fried chicken wings.
h. Patient's sleep habits	Mr. Platt sleeps no more than 7 hours on nights when he helps his children with homework. He usually goes to bed at 11 pm and awakens at 6 am for work or to help get the children off to school.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	An annual medical examination identified a vitamin D deficiency. His blood pressure and fasting glucose levels are normal, but his father and grandfather both had type 2 diabetes that eventually required insulin. He takes a daily multivitamin supplement that contains 800 IU of vitamin D ₃ .
j. Allergies	NKA
k. History of other adverse reactions to medications	Penicillin skin reaction as a child
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary	Mr. Platt is a reasonably healthy man, although he is still overweight with a BMI of 26.3 kg/m ² . He desires to lose weight and hopes to improve his running endurance so that he can complete a 26-mile marathon.

problem(s).	
3. Identify exclusions for self-treatment.	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Calculate a sweat rate. Mr. Platt's target marathon is planned for November. Dehydration risk should be minimal. His current sweat rate is 0.8 kg per hour in warm conditions. With his marathon in cooler conditions, he can train to replace half of his fluid losses by drinking 360 ml of fluid per hour. He can target 90 mL (3 oz) of water every 15–20 minutes. Mr. Platt will wear a waist belt with a small pouch and a detachable 8 oz bottle that he can refill from water stations. (2) The marathon will provide water and Gatorade sports drink. Mr. Platt can prepare a calorie-free electrolyte drink from an easy-to-carry wafer (Nuun) mixed with water available on the course. His goal is to drink 360 mL (12 oz) per hour, so he will prepare a bottle with $\frac{1}{2}$ of a wafer added to 6 ounces (180 mL) of water every 30 minutes. Mr. Platt can sip on this drink while running, rather than drinking larger volumes at each water station. Each wafer (2 bottles) will provide 360 mg sodium and 100 mg potassium per hour. These amounts are greater than the sports drink provides. (3) Mr. Platt can consider a mixed approach where he trains for 90–120 minutes in his aerobic zone without carbohydrate intake before introducing small amounts of carbohydrate in the later stages of training. He can train with the carbohydrate–electrolyte sports drink the race will provide. Following the same fluid consumption rate (360 mL per hour) will provide 22 g carbohydrate per hour. This is less than the guideline recommendations for 30–60 g per hour, but his primary goals are finishing the marathon distance while improving his body weight. (4) Mr. Platt can follow the original calorie-free electrolyte water plan but introduce a carbohydrate–electrolyte with added protein source such as Accel-Gel. Each gel packet provides 20 g of carbohydrate and 5 g of protein as a secondary fuel for the exercising muscle. Mr. Platt can plan

	to use ½ of a gel packet every 15 minutes starting 90–120 minutes into the marathon. This will provide 40 g carbohydrate and 200 mEq sodium per hour. When introducing the gel, he should switch to plain water at a goal rate of 360 mL per hour.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Mr. Platt should train for 90 minutes using a water–electrolyte solution and then introduce a gel that provides carbohydrate and electrolytes with added protein starting around 90 minutes.
6. Describe the recommended therapeutic approach to the patient or caregiver.	“Your training plan indicates that your longest training runs will be 3.5 hours in duration. You can train the first 90 minutes using a noncalorie sports drink, and then add carbohydrates and protein to help sustain your efforts and support endurance. Your primary goal will be to optimize fat utilization as a primary fuel in all of your runs long runs. Taking ½ of a gel packet every 15 minutes will provide 40 g of carbohydrate and 200 kcal per hour. You will need water available at the race course to dilute the concentrated gel. The gel also will deliver sodium (200 mEq per hour), so you can switch your hydration to plain water at 360 mL per hour. The packets are lightweight and easily carried in a pouch that is attached to the same belt that holds the refillable water bottle. You should introduce the gel packets into your training now, so that you can evaluate your tolerance to the gel in training conditions.”
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	“For the first 90 minutes of your long training runs, the focus is on fatty acid oxidation and its effect on weight reduction. After 90 minutes, you can introduce a carbohydrate and protein source as additional fuels for continued effective muscle contraction. The amount of calories consumed is around 200 kcal per hour, which is less than the anticipated caloric burn rate for running at 8–10 miles per hour. The goal is to burn primarily fat for energy, while providing some energy to support your ability to finish. The carbohydrate doses are small and should not have a negative effect on fatty acid oxidation since your pace will remain within your aerobic threshold. The calories in the sports gel will not impair your primary weight loss plan. A secondary benefit may be a reduction in muscle soreness the

	day after long training runs by introducing a protein source as a noncarbohydrate source of energy.”
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
a. Appropriate dose and frequency of administration	“Current guidelines recommend an intake of 30–60 g of carbohydrate per hour. Consumption of 2 packets of sports gel will provide 40 g of carbohydrate per hour.”
b. Maximum number of days the therapy should be employed	“You only need to use the carbohydrate-electrolyte with added protein sports gel on your long-run training days that will exceed 90 minutes. In general, this is only one run per week. The other runs should start in a fasted state to optimize fatty acid metabolism. You should carry a gel product on shorter runs (45–90 minutes) to address any symptoms of a low blood sugar.”
c. Product administration procedures	“Several calorie-free electrolyte drinks are available, but the most convenient method may be to carry a wafer that dissolves in water. This product can be used in your routine training (less than 90 minutes) so that you grow accustomed to its taste, tolerance, and mixing process. The tablets can be cut in half in advance. They come in a plastic tube that will prevent them from breaking down while running.”
d. Expected time to onset of relief	“Continued training without carbohydrate intake should be associated with additional weight loss. Training benefits should be seen as your total body weight decreases, although this process takes months. The inclusion of a carbohydrate sports gel, starting after 90 minutes of training, is likely to produce a subjective feeling of additional energy from the first dose. Repeated doses will be needed to provide additional carbohydrate calories as they are used. Despite the feeling of additional energy, the actual impact on performance measures such as pace per mile or total miles run will be

	difficult to prove. The intent is to focus on the goals to complete the full distance of each long training run (up to 18 miles) in anticipation of finishing the marathon, rather than being concerned about how fast it is finished.”
e. Degree of relief that can be reasonably expected	“Finishing the marathon is one primary objective, but losing weight to a healthier BMI is an equally important objective. The addition of carbohydrate and protein only on long runs should help you reach both objectives. The additional calorie sources on long runs will help your body extend endurance and improve the total duration and length of these runs. A reasonable expectation is to increase total distance run per week by 5%–10% each week.”
f. Most common adverse effects	“Consuming calories during continued exercise takes practice but most endurance athletes can adapt. Gastrointestinal discomfort such as bloating and cramping are common during early experiences with sports drinks and gels. Nausea and diarrhea have been reported. Be sure to drink plenty of fluids to allow the nitrogen waste from the protein to be eliminated through your kidneys.”
g. Adverse effects that warrant medical intervention should they occur	“During any period of increased training, you should always tell your coach or training partner if you are not feeling well. Any signs of heat illness, muscle cramping, or pain on urination should be reported immediately.”
h. Patient options in the event that condition worsens or persists	“If you are unable to tolerate the sports gel with protein, consider a similar gel that provides only carbohydrate.”
i. Product storage requirements	“Electrolyte wafers and unopened gel packets can be stored at room temperature. A reconstituted electrolyte drink and any open gel packets should be used within 2 hours, or discarded. Electrolyte wafers are hygroscopic and can absorb water from the air over time, although it takes weeks for them to degrade. If you live in a humid environment, the wafers will last longer when stored in environmentally controlled conditions.”
Solicit follow-up questions from the patient or caregiver.	“Why are you recommending a sports gel that includes protein? None of my training partners are using it. They drink Muscle Milk after their long runs. Why are you not recommending that product?”

Answer the patient's or caregiver's questions.	"Sports drinks with added protein may be associated with less muscle discomfort the day following each long athletic effort. You have commented on muscle soreness at work the day after long training runs. Comparison studies were conducted in long-distance cyclists riding for several hours on stationary bikes. When carefully controlled to provide equal calories, the protein-included sports drink did not affect performance but was associated with lower creatine kinase levels in the blood and subjective reports of less muscle soreness the day after the trial. You may perceive a benefit if your next-day muscle soreness is reduced. Muscle Milk is advertised as a recovery drink. This product is manufactured to contain whey protein from milk with small amounts of added sugar and fat for taste. The nutrition content label will indicate more protein and less carbohydrate and sugar than for equal volumes of low-fat milk, although its price can be 3-4 times higher. Muscle Milk was not tested by Consumer Lab.com in its last protein drink review. Low-fat milk as part of a meal, however, is an evidence-based choice for rehydration and recovery."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Mr. Platt within 2-3 weeks to review his progress with the training plan and tolerance for the recommended products. Consider referral to an RD or RDN if any additional questions arise regarding Mr. Platt's diet and nutritional requirements.

Key: BMI = Body mass index; ICU = intensive care unit; n/a = Not applicable; NKA = no known allergies; RD = registered dietitian; RDN = registered dietitian nutritionist.

Case 25-2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	

1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient is a high school football player who complains of fatigue and tired legs, starting about 30–40 minutes into his team workouts. He is currently participating in summertime preseason workouts and has 9 practices a week, with 2 workouts daily on Mondays, Wednesdays, and Fridays. He reports a decrease in leg strength, particularly when asked to push a heavy blocking sled. He also notes a decrease in running speed when doing 40-yard shuttle runs on the field. He comments that white lines of salt are visible on his clothing when it dries. Despite this observation, he thinks that he cannot be dehydrated, because he has to urinate frequently and he wakes from sleep at least once a night to urinate.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Summer workouts take place in high temperatures and humidity. For this patient, the fatigue sets in earlier under direct sunlight. Rehydration halfway through practice improves leg strength for 10–15 minutes. By comparison, air-conditioned training does not result in fatigue. The indoor workout focuses on strength and balance as well as walking through plays, so the intensity and energy expenditure are lower. When asked, he says that he does not drink a sports drink before indoor workouts, because he does not anticipate the same level of thirst.
c. Description of the patient's efforts to relieve the symptoms	The athletic trainer at the school is active in weighing the athletes before and after practice. The patient had a 4-pound weight loss over 2 practices, and the athletic trainer calculated a fluid replacement goal of 1800 mL (60 ounces) per day. On the advice of his coach, the patient drinks a full 20-ounce bottle of carbohydrate–electrolyte drink 3–5 times a day (1800–3000 mL daily). He drinks half of the bottle (10 ounces) at the start of practice and the rest during a 10-minute break halfway through practice. He drinks a second bottle immediately after the workout. On days with 2 workouts, he drinks 4 bottles. He finishes each day with an additional bottle before bed.
d. Patient's identity	Ryan Ladone
e. Patient's age, gender, height, and weight	17 years, male, 6 ft 0 in., 220 lb

f. Patient's occupation	High school student
g. Patient's dietary habits	Ryan has been eating larger portion sizes to gain weight for football season. The family eats some sort of fast food for dinner at least 3 nights a week. When meals are cooked at home, they are healthy meals.
h. Patient's sleep habits	He gets 8 hours of sleep each school night but complains of sleep interruptions for urination.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Ryan's preseason laboratory results included a fasting blood glucose of 110 mg/dL and HbA _{1c} of 6.1%, which suggest that he may have glucose intolerance. His current BMI is 29.8 kg/m ² , which is approaching obesity. Ryan is at risk for adult-onset diabetes. His blood pressure was 105/70 mm Hg at his primary care provider's office. Ryan takes no scheduled medications or supplements.
j. Allergies	NKA
k. History of other adverse reactions to medications	None reported.
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Ryan is experiencing a decline in muscle endurance (over 90 minutes) associated with a post-exercise loss of 1.8% of his body weight. He is likely feeling the effects of dehydration. He also may be experiencing the metabolic effects of a pre-exercise carbohydrate load. The resulting insulin release may be causing a reduction in fatty acid oxidation, leaving Ryan more dependent on carbohydrate energy during the long workout. His fatigue is temporally associated with rapid glucose utilization and is relieved after midsession rehydration with additional carbohydrates.
3. Identify exclusions for self-treatment.	Ryan's father has type 2 diabetes. A family history of diabetes may complicate Ryan's decision to use a sports drink, and he is drinking a large quantity of carbohydrate-containing product per day.
4. Formulate a comprehensive list of therapeutic	Options include (1) Take no action. Symptoms may abate when school starts and the number of practices is reduced to once per day.

alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Dehydration also is less likely with cooler weather and less direct sunlight in late September and October. (2) To monitor dehydration, a simple daily weight taken in the morning (before any exercise or nutrition intake) can assist in monitoring for changes in body weight. Changes in weight are a secondary marker of hydration status. The goal is to start each day with a stable weight and hydration status. (3) Increase dietary salt intake during the training season, with appropriate amounts of free water to replace sweat losses. The targeted fluid replacement of 60 ounces (1800 mL) was based on a day with 2 outdoor workouts of roughly 4 hours. Consider drinking 12 ounces (360 mL) of water per hour of continued exercise and an additional 12 ounces after exercise. Sodium can be provided with his regular meals along with salty snacks after workouts. (4) Consider using noncaloric Nuun wafers or low-calorie G2-Gatorade during workouts. One wafer mixed in 12 ounces of water will provide 160 mEq of sodium without carbohydrate. G2 will provide a similar amount of sodium with only 8 g of carbohydrate. (5) After each workout, consider drinking low-fat milk rather than a sports drink. Consuming low-fat milk for recovery has been associated with better rehydration during the 4 hours after a workout, as evidenced by less urine output when compared to the sports drink and improved replacement of body weight loss to dehydration.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Taking 1–2 days off from practice (Saturday and Sunday) will allow time to help reestablish normal hydration and a baseline body weight. Monitor weight daily, first thing in the morning, as a secondary measure of hydration status. Weight loss of 1 kg (2.2 lb) in a day is suggestive of water loss of 1000 mL. Attempt to start each day at about the same body weight. Monitor urine for a light yellow color. Dark yellow to brown urine is suggestive of dehydration. Mix a no-calorie electrolyte sports drink using an electrolyte wafer. The wafers are lightweight and portable and are dissolved in water available during practice. The wafer provides an appropriate product to use before and during the first hour of practice. If

	fatigue sets in after 60–90 minutes of practice, a carbohydrate sports drink is reasonable to assist in completing the workout. For recovery after practice, 8–16 ounces (240–480 mL) of low-fat milk with a meal or salty snack is better for recovery than a sports drink. Ryan should not consume an additional 20-ounce sports drink before bed.
6. Describe the recommended therapeutic approach to the patient or caregiver.	“Your weight loss during practice is 1.8% of your total body weight. Clinical dehydration with reduced performance is common in athletes who lose 2% of their body weight per exercise session. Focusing on post exercise recovery, rehydration, and glycogen replacement is reasonable.”
	“A salty meal or snack has been recognized to assist in recovery and rehydration after exercise. Consuming a meal that is balanced with protein, fat, and carbohydrate, preferably complex carbohydrate, generally is superior to sports drinks.”
	“Low-fat milk is an excellent source of all three macronutrients as well as sodium and potassium in quantities exceeding that of sports drinks. Low-fat milk also has been superior to sports drink in replacing body weight lost due to exercise-induced dehydration. The volume of urine output following a sports drink is considerably larger than the volume of urine produced by an equal volume of milk. You have commented on sleep interruption related to drinking a sports drink at night before bed. Milk may be a better choice to retain fluid, with fewer trips to the bathroom.”
	“The sports drink that you are using is a significant source of high-glycemic-index carbohydrate. A daily total of 60 ounces from three bottles will provide 105 g of carbohydrate. You are consuming even more carbohydrate after twice-daily practices. Your current weight and BMI suggest that you are overweight. Your fasting glucose levels indicate that you are at risk for developing insulin resistance and type 2 diabetes. Minimizing exposure to high-glycemic carbohydrates is reasonable.”
	“You should avoid carbohydrate intake in the 2 hours before exercise to allow your body to optimize its ability to use fatty acids for energy during aerobic exercise. Your workouts have long periods of aerobic recovery between short, high-intensity bursts. You may find that your endurance is improved by optimizing fat burning over carbohydrate dependence. Use of a sports drink after 60–90 minutes of practice is reasonable if your total workout time exceeds 10–15 hours per week.”
	“A carbohydrate dose before exercise is known to stimulate insulin release, which moves the carbohydrates into the exercising muscle cells. This insulin release inhibits the enzymes that help to break down serum

	triglycerides, significantly reducing your ability to oxidize fatty acids. Normally, aerobic oxidation of fats contributes at least 50% of your energy needs on the field of play. Drinking a carbohydrate sports drink before exercise may be reducing your ability to use fats for energy and may be influencing your muscles to use carbohydrates for all energy needed on the field. This may explain why you get fatigued quickly, and why a carbohydrate drink during the break may lead to a short recovery. This reaction to carbohydrates can occur in certain athletes who are more sensitive to carbohydrate doses, but it is not the case for all athletes.”
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	“Providing a healthy meal within 2 hours after exercise is the optimal way to replace muscle glycogen and restore hydration balance. The typical American diet has sufficient salt for replacement of salt losses. Your experience of poor performance occurs after drinking a carbohydrate sports drink and participating in mixed aerobic/anaerobic activity of variable intensity. You have noted a loss of performance over time (60 minutes) and a recovery after a supplemental dose of carbohydrate at mid-practice. The recovery lasts only 15–20 minutes. This suggests that your performance is affected by carbohydrate availability, rather than fatty acid oxidation, during sustained exercise.”
	“Low-fat milk is an excellent source of all three macronutrients as well as sodium and potassium in quantities exceeding that of sports drinks. Low-fat milk also is superior to sports drinks in replacing body weight lost with exercise-induced dehydration. The volume of urine output after consuming a sports drink is considerably larger than the volume of urine produced after drinking an equal volume of milk.”
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
a. Appropriate	“A 12-ounce bottle of water with an electrolyte wafer added will provide

dose and frequency of administration	360 mg of sodium to support hydration during the first hour of practice. Drinking 3 ounces (90 mL) every 15 minutes ensures that the sodium is available slowly during practice. Additional water is permitted if you are thirsty."
	"Sports nutrition guidelines recommend the use of a carbohydrate sports drink only when exercise time exceeds 60-90 minutes. If fatigue sets in after 60 minutes, you can switch to drinking 150 mL (4 ounces) every 15 minutes using a carbohydrate sports drink like Gatorade. This strategy will provide 36 g of carbohydrate for each hour of sustained practice. Gatorade Thirst Quencher is available in a 20-ounce bottle that provides this specific amount of carbohydrate and fluid."
b. Maximum number of days the therapy should be employed	"Dehydration will be most common on days of multiple workouts, and glucose for energy will be needed mostly during the preseason, when workouts last several hours. A sports drink will be less necessary when school starts, workouts are shorter in duration, and the season changes, bringing cooler weather. There is no reason to use a sports drink during the off season."
c. Product administration procedures	n/a
d. Expected time to onset of relief	n/a
e. Degree of relief that can be reasonably expected	"Some athletes have higher sensitivity to insulin release than others. Avoiding carbohydrates in the 2 hours before practice will allow you to start each practice in a metabolic state optimized for use of fatty acids for your primary fuel at aerobic intensities. When intensity increases, you will have adequate stores of muscle glycogen to provide fuel for 60-90 minutes of the workout and maybe longer. It is possible you will feel some difference in the first few workouts on the new fueling strategy. However, adaption to fatty acid metabolism as a primary fuel will take multiple workouts and possible several weeks of sustained training."
f. Most common adverse effects	"It is unlikely that the electrolyte wafer will cause any adverse effects that you have not experienced from drinking a carbohydrate sports drink during practice. The wafers are effervescent and release a very small amount of carbon dioxide gas while they dissolve. The gas can be vented off by not sealing the bottle during the 5 minutes of tablet dissolution. Failure to allow the gas to release may lead to slight stomach bloating from the wafer product. Otherwise, the wafer is not expected to cause adverse effects that are different from what you have experienced from the sports drink."

g. Adverse effects that warrant medical intervention should they occur	“You should see your regular health care provider if you are unable to return to your usual morning weight, or if you experience muscle cramping that persists despite adequate salt intake. You mention lines of sweat on your clothes. If cramping occurs frequently or is severe enough to interrupt practice, it would be reasonable to see your provider for measuring serum levels of calcium and magnesium as well as testing kidney function. Similarly, if you notice that your urine is significantly darker than usual or has a new foul odor, first assess your hydration status. If the urine changes are persistent despite proper hydration, you will want to follow up with your regular health care provider.”
h. Patient options in the event that condition worsens or persists	“If you observe a dark urine that is not normalizing with proper hydration, you can elect to reduce the protein in your diet for a few days. If the color or odor persists, then consider seeing your regular health care provider.”
i. Product storage requirements	“Electrolyte wafers and unopened sports drinks can be stored at room temperature. A reconstituted electrolyte drink and any open sports drinks should be used within 2 hours or discarded. Electrolyte wafers are hygroscopic, so they can absorb water from the air over time. The wafers will last longer in storage conditions that are environmentally controlled.”
Solicit follow-up questions from the patient or caregiver.	“I have read that creatine is natural and safe. Do you think that creatine would improve my performance?”
Answer the patient's or caregiver's questions.	“Creatine is a naturally occurring compound found in red meats and fish. Choosing natural sources of creatine from dietary protein is ideal, particularly, because taking creatine supplements has been associated with unintended adverse effects. Creatine supplements have not been proved to be more effective than natural dietary creatine in building muscle mass. In addition, misbranding of nutrition supplements has occurred, by either intentional or unintentional formulation. You should use natural protein sources when possible. If you choose to use a supplement, at least narrow your choice of supplement to a product that has undergone quality assurance testing by an independent laboratory.”
Follow-up: Monitor and Evaluate	
9. Assess	Contact Ryan and his parents within 1 week to determine whether he has

patient outcome.	made an appointment with his primary care provider.

Key: HbA_{1c} = Glycosylated hemoglobin; n/a = not applicable; NKA = no known allergies.

Patient Counseling for Performance-Enhancing Nutrients

The quest for enhanced physical performance has resulted in serious health consequences for some athletes. Clinical studies of many botanical and hormonal dietary supplements touted as performance-enhancing products reveal significant adverse effects and little or no enhancement in physical performance. Health care providers should discourage use of performance-enhancing products, because none except creatine has been found to be effective. The box “Patient Education for Performance-Enhancing Nutrients” lists specific information to provide in patient counseling.

Registered dietitians with national board certification as Certified Specialist in Sports Dietetics are uniquely qualified to assist athletes of all levels in evaluating their nutritional needs and to work with them on hydration needs, as well as the quality, quantity, and timing of foods and supplements for optimal performance. Accredited sports dietitians can be found on the Sports, Cardiovascular and Wellness Nutrition web site (www.scandpg.org).

Patient Education for Performance-Enhancing Nutrients

The objective in selecting a performance enhancer is to choose a product

that is safe and appropriate for the type, intensity, and duration of the physical activity. Following the recommendations of an appropriate health care provider and other sports nutrition specialists, as well as carefully following product instructions and the self-care measures listed here, will help ensure optimal therapeutic outcomes.

Muscle Glycogen Preservation

- Carbohydrate-containing sports drinks contain one or more forms of sugar and the electrolytes sodium and potassium. These drinks are optimal for practice or training sessions that last longer than 90 minutes and are generally not needed during the first 60–90 minutes of training. Small doses repeated every 15–20 minutes may be necessary for sustained energy over longer events to maintain glucose levels for performance energy, thereby delaying the time to fatigue.
- Athletes with diabetes should seek the advice of a knowledgeable health care provider or sports dietitian before beginning an exercise program to ensure that they are prepared to avoid hypoglycemia while exercising.
- Note that sports bars often contain other macronutrients, such as fats and proteins. Many of these bars are more appropriate for after-exercise recovery than for use during athletic events. If a well-balanced meal is unavailable within 2 hours of exercise completion, many of these bars may be an appropriate after-exercise fuel replenishment source. (Table 25–1 lists specific products.)
- Long-chain triglycerides can cause discomfort and bloating during intense exercise; therefore, avoid consuming meals that contain large amounts of fat at least 2 hours before exercise.

Enhancement of Muscle Mass

- Athletes do not need to exceed the recommended daily intake of 2.0 g of protein per kg of body weight to increase body mass. Available data indicate that higher intakes do not produce additional muscle mass or strength.
- Athletes who ingest high amounts of protein, either through their

foods or protein supplements, should discuss this practice with their regular health care provider or sports dietitian. Blood urea nitrogen and serum creatinine levels may be monitored to ascertain whether high-protein intake is affecting kidney function.

Hydration and Electrolytes

- For athletes exercising less than 60–90 minutes, water intake alone is sufficient to complete the exercise.
- Athletes exercising longer than 60 minutes may consider incorporating a carbohydrate- and electrolyte-containing sports drink into the exercise program for optimal performance.
- Endurance athletes exercising for 4 hours and longer are discouraged from drinking only free (regular) water owing to the risk of dilutional hyponatremia. Exercise of this duration (e.g., marathon running, long-distance triathlons) will require electrolyte and carbohydrate replacement for optimal performance.
- Athletes should not target a set quantity of water to consume during exercise; rather, they should drink according to the trigger of thirst. Slower runners and walkers exercising in cool conditions can consume water at a lower rate (sips), whereas faster and heavier athletes and those exercising in heat and humidity should be prepared to drink a large volume. Individual calculations of sweat rate for fluid needs during exercise and an additional calculation for recovery fluids can be made to better meet the athlete's needs.
- Athletes should consume 6–12 ounces of plain water if exercise lasts less than 60 minutes. If exercise lasts longer than 60 minutes, they should consider a carbohydrate- and electrolyte-containing sports drink. (See *Fluid Tips for Training and Competition*, available at <http://arizona.openrepository.com/arizona/bitstream/10150/146640/1/az1387-2006.pdf>.)
- Carbonated water may cause gastrointestinal distress and bloating; avoid drinking carbonated water before or during an athletic event.

Ergogenic Supplements

- Little or no clinical evidence supports the performance-enhancing

claims of most herbal supplements. Quality concerns, misbranding, and contamination with heavy metals have occurred with sufficient frequency to suggest that risk outweighs benefit and that such supplements should be avoided.

- Creatine may help increase muscle strength and power in events that require short bursts of power, but gastrointestinal discomfort may occur. To avoid this problem, do not take loading doses. The same benefits occur within 7–14 days of taking a daily maintenance dose of 5 g daily. Maintain proper hydration to assist in the elimination of metabolic waste and to avoid dehydration.
- Long-term use of creatine has no known benefit. The strength improvements achieved with creatine are not maintained beyond the period of supplementation; on cessation of creatine intake, “washout” will occur, with reversion to baseline values. Athletes should consider optimizing their nutritional intake rather than using creatine.

Key Points for Sports Nutrition and Performance-Enhancing Nutrients

- Training regularly and eating a well-balanced diet are consistently shown to benefit sports performance and activity. Most athletes do not require sports nutrition products.
- Despite marketing claims, the benefits of most performance-enhancing nutritional products and ergogenic aids are unproved, and several may be unsafe.
- Misbranding of nutritional supplements has occurred and can lead to unintentional safety risks and to positive results on screening tests performed by antidoping agencies.
- Most sports nutrition drinks, gels, and bars are significant sources of carbohydrate calories. AAP has developed a position that these

carbohydrate and energy drinks should not be used in adolescents and children. They should similarly be avoided in adults who are not engaging in prolonged bouts of exercise (>60–90 minutes).

- Dehydration can significantly affect performance. However, no evidence supports sports nutrition drinks as beneficial when used during events lasting 60 minutes or less. For activity longer than 60 minutes, electrolytes in carbohydrate-containing sports drinks are encouraged and may enhance fluid absorption.
- Sports nutrition drinks containing carbohydrates and electrolytes can prolong the time to fatigue (glycogen depletion) in events or practices lasting 60–90 minutes or longer. Use of such sports drinks may therefore be considered when exercise duration is anticipated to exceed this duration.
- To minimize the risk of dehydration or hyponatremia related to the intake of salt-free fluids, athletes exercising for very long periods of time should use sports drinks that contain electrolytes and carbohydrates rather than plain water.
- Creatine supplementation can increase muscle phosphocreatine concentrations, thus increasing the amount of stored energy in muscles. Phosphocreatine can lend its high-energy phosphate bond to ADP to rapidly restore ATP, allowing increased power for single bursts and repeated activities of high intensity for 30 seconds or less.
- Pseudoephedrine is monitored by the U.S. Anti-Doping Agency, and athletes subject to testing for banned substances should be warned about any product containing this substance. A similar warning should be given for any cough and cold product that includes a sympathomimetic amine as a decongestant, such as oxymetazoline nasal spray.

Chapter 26: Infant Nutrition and Special Nutritional Needs of Children

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Human milk is most physiologically suited to infants and is their optimal milk source up to the age of 12 months. The American Academy of Pediatrics (AAP) recommends that human milk be used as the sole source of nutrition for infants during the first 6 months of life. For infants whose mothers choose not to breastfeed, the nutritional quality, safety, and convenience of infant formulas make such products an appropriate alternative. Variations among formulas allow for product selection to meet a specific infant's nutritional needs, along with considerations of palatability, digestibility, nutrient sources, convenience, and cost.

In the area of infant nutrition, an important role for today's pharmacist is as an additional information resource for parents or other caregivers to promote successful breastfeeding. In addition, in consultation with the child's parents and primary care provider, the pharmacist also can evaluate indications, advise on formula selection, and help ensure its appropriate use. This service requires in-depth knowledge about infant and child nutrition needs, breastfeeding issues and practices, and commercially prepared infant and pediatric formulas, including differences in formula composition and specific uses for therapeutic formulas.

Some children may require specialized enteral formulas after the age of 1 year because of various disease states and conditions. Familiarity with these products and their appropriate use is essential to allow the pharmacist to answer related caregiver questions, facilitate their procurement, and perform an assessment for associated complications.

Organ Maturation and Infant Growth

Knowledge of the development of the gastrointestinal (GI) tract and the kidney is crucial to understanding infant nutrition. Different aspects of maturation are reflected in physiologic parameters and events of digestive function, as reviewed in this section.

In clinical practice, monitoring growth and growth rate using World Health Organization (WHO) growth charts is important for assessing the infant for possible abnormal or unhealthy growth. WHO growth charts are recommended for use in children younger than 24 months of age, and the Centers for Disease Control and Prevention (CDC) growth charts are recommended for use in children 24 months and older.¹

Gastrointestinal Maturation

By the completion of 27 weeks of gestation (or 27 weeks after the woman's last menstrual period), all segments of the fetal GI tract are formed and display some physiologic function. From 28 weeks of gestation onward, however, maximal GI tract growth and differentiation occur. Therefore, premature infants—those born before 37 weeks of gestation—often have reduced GI tract function, especially those born before 32 weeks. Transition from intrauterine nutrition delivered through the maternal–fetal unit (i.e., the placenta) to extrauterine nutrition derived from mother's milk or infant formula requires the maturation of many physiologic processes. These processes include effective sucking, swallowing, gastric emptying, intestinal peristalsis, and defecation; production of salivary, gastric, pancreatic, and hepatobiliary secretions; and development of intestinal brush border enzymes and transport systems ([Table 26–1](#)).²

Table 26–1 Gastrointestinal Maturation

Function	Weeks of Gestation When First Detectable	Comments
Sucking and swallowing	16	16weeks: swallowing of amniotic fluid
		26 weeks: sucking
		33–35 weeks: mature, coordinated sucking, swallowing, and breathing
Gastric motility and secretion	13	Gastric emptying delayed in first few days of life; affected by caloric density, carbohydrate concentration, pathologic conditions
Intestinal motility	20	26–30 weeks: disorganized contractile activity

		30–34 weeks: repetitive groups of contractions
		34–35 weeks: more mature migrating motor complexes
Digestion and Absorption		
Important Factors	Weeks of Gestation When First Detectable	Proportion of Adult Values
Protein		
Enterokinase	24–26	30 weeks: 20%
		Term: 10%–25%
Hydrochloric acid	At birth	30 weeks: <20%
		Term: <30%
		First 3 months: 50%
Peptidases	<12	30 weeks: 15%
		Term: nearly 100%
Trypsinogen/ chymotrypsinogen	20	Term: 10%–60%
Amino acid transport	ND	Term: nearly 100%
Macromolecule absorption	ND	Term: nearly 100%
Fat		
Lingual lipase	30	Term: nearly 100%
Pancreatic lipase	16–20	Term: 5%–10%
Bile acids	22	32 weeks: 25%
		Term: 50%
Medium-chain triglyceride uptake	ND	100% (absorption occurs in the stomach)

Long-chain triglyceride uptake	ND	<i>Term:</i> 10%–90%
Carbohydrate		
Pancreatic alpha-amylase	22–30	<i>Term:</i> 0%
		<i>6 months of age:</i> secretion begins
Salivary alpha-amylase	16	<i>30 weeks:</i> 0%
		<i>Term:</i> 10%–20%
Lactase	11	<i>28–34 weeks:</i> 30%
		<i>Term:</i> nearly 100%
Monosaccharide absorption	11–19	<i>Term:</i> glucose absorption: 50%–60%

Key: ND = Not determined.

Source: [Reference 2](#); Kleinman RE, Kamin DS. Gastrointestinal development. In: Baker SS, Baker RD, Davis AM, eds. *Pediatric Nutrition Support*. Sudbury, MA: Jones & Bartlett; 2007:15–27; Dienhart M, Yacob D, Balint J. Gross digestion principles: gastric grinding and gastrointestinal motility. In: Corkins MR, Balint J, Bobo E, et al. eds. *The A.S.P.E.N. Pediatric Nutrition Support Core Curriculum*. 2nd ed. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2015:15–22; and May TD, Shulman RT. Carbohydrates: changes with development. In: Corkins MR, Balint J, Bobo E, et al. eds. *The A.S.P.E.N. Pediatric Nutrition Support Core Curriculum*. 2nd ed. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2015:23–29.

Nutritive sucking develops at approximately 33–34 weeks of gestation. In term infants born at 37–42 weeks' gestational age, a mature, efficient pattern of sucking is seen within a few days after birth. In premature infants, an immature, inefficient pattern may persist for a month or longer. Infants born before they attain a gestational age of 34 weeks cannot coordinate sucking, swallowing, and breathing and may therefore require tube feedings for several

weeks to months until these reflexes mature. Liquid nutrition is appropriate for all infants until complex tongue movements and swallowing reflexes mature. Maturation of these reflexes typically occurs by the age of 4–6 months, and it is at this time that solid foods can be safely added to the infant's diet.² For infants born prematurely, corrected gestational age should be used to determine these developmental milestones. *Corrected gestational age* is calculated by adding chronologic age to gestational age at birth. Once premature infants reach 40 weeks corrected gestational age, their growth and developmental parameters are assessed using an age adjusted for gestational age (i.e., chronologic age in weeks minus number of weeks premature). For example, for an infant born at 23 weeks' gestational age who is currently 25 weeks old, the corrected gestational age would be 48 weeks, with a maturation age of 2 months (or 8 weeks) corrected age. This patient would therefore be developmentally equivalent to a term infant at 2 months of age.

Early in life, frequent feedings (every 2–3 hours) are necessary, because the stomach capacity of a term newborn with a birth weight greater than 2500 g (5 pounds 8 ounces) is only 20–90 mL (equivalent to approximately 0.7–3 ounces). Gastric capacity increases to 90–150 mL (3–5 ounces) by 1 month of age, at which time longer periods between feedings are possible, enabling the infant to sleep for longer periods of time (i.e., through the night). Human milk empties more rapidly from the stomach than infant formula; therefore, human milk–fed infants typically eat more often than their formula-fed peers.

In term infants, gastric acid and pepsin secretion peak in the first 10 days of life, decrease between 10 and 30 days of life, and then increase to adult levels by the age of 3 months. In premature infants, basal acid output is lower than that in term infants but increases with postnatal age. Milk in the infant's stomach causes a sharp increase in the pH of the gastric contents and a slower return to lower pH values than in older children and adults. Gastric acidity in the newborn is unsuitable for optimal pepsin action. Because of this low pepsin activity, little protein digestion occurs in the stomach. The extent of protein absorption, however, is similar to that seen in children and adults. Amino acids and peptides produced by protein digestion are absorbed passively or by active transport mechanisms that reach adult capacity by the age of 14 weeks.

Premature and full-term infants can digest most carbohydrates, because the production of intestinal enzymes such as sucrase, maltase, isomaltase, and

glucoamylase is sufficiently mature at birth. Lactase activity increases relatively late in fetal life and begins to decline after the age of 3 years, especially in African American children and those of Asian ancestry. By adulthood, approximately 15% of Whites, 40% of Asian Americans, and 85% of African Americans are deficient in intestinal lactase.³ Pancreatic amylase secretion does not reach adult levels until the age of approximately 1 year. Salivary amylase may help compensate for this relative lactase and amylase deficiency in early infancy. Despite this relative lactase deficiency, most term and preterm infants tolerate lactose-containing formulas, with negligible unabsorbed carbohydrate output in the stool. Unabsorbed lactose that enters the colon undergoes bacterial fermentation (colonic salvage) to short-chain fatty acids, thereby creating an acidic environment that favors growth of acidophilic bacterial flora (lactobacilli) and suppresses growth of more pathogenic organisms. This acidity also promotes water absorption and prevents osmotic diarrhea. Because of the relative abundance of glucoamylase compared with lactase in the premature infant's intestine, glucose polymers are digested and absorbed better than lactose is.²

Newborns exhibit low concentrations of pancreatic lipase and slow rates of synthesis of bile acid. Both pancreatic lipase and bile acids are important for fat absorption. The rate of bile acid synthesis increases throughout gestation and with increasing postnatal age. The bile acid pool in a premature infant is one-fourth that in an adult, whereas a term infant's is one-half that in an adult. However, fat malabsorption is not a major problem in preterm or term infants, because lingual and gastric lipases are present. Infants born earlier than 34 weeks' gestational age, however, may exhibit steatorrhea.

Intestinal length also may affect nutrient absorption. At birth, a term infant's small intestine is approximately 270 cm (106 inches) long. From 28 weeks' gestational age, the intestinal length approximately doubles. Infants born prematurely, therefore, have less small intestine and consequently a decreased surface area for absorption. Adult intestinal length of 4–5 m (13–16.5 feet) is reached by the age of approximately 4 years.

Kidney Maturation

Maturation of the kidney also is important in nutrition because it determines the ability of the kidney to excrete a solute load. Glomerular filtration begins around week 9 of fetal life; however, kidney function does not appear to be

necessary for normal intrauterine homeostasis, because the placenta serves as the major excretory organ. After birth, the rate of glomerular filtration increases until growth stops, toward the end of the second decade of life. Even after correction for body surface area, the glomerular filtration rate in children does not approximate adult values until the third year of life.

Growth

Birth weight is determined primarily by maternal prepregnancy weight and pregnancy weight changes. The average birth weight of a term infant is approximately 3500 g (7 pounds 11 ounces). Premature infants are categorized by birth weight as follows: *low-birth-weight* infants weigh less than 2500 g (5 pounds 8 ounces); *very low-birth-weight* infants weigh less than 1500 g (3 pounds 4 ounces); *extremely low-birth-weight* infants weigh less than 1000 g (2 pounds 3 ounces); and so-called *micropreemies* weigh less than 750 g (1 pound 10 ounces).

Water weight loss (6%–10% of body weight) occurs immediately after birth over a period of 1–2 weeks. Subsequently, the average weight gain throughout the first 12 months of life is 26–31 g daily for the first 3 months; 17–18 g daily for months 3–6; 12–13 g daily for months 6–9; 9 g daily for months 9–12; and 7–9 g daily from 12 months of age.⁴ Most term infants double their birth weight by 4–6 months of age and triple it by 12 months. Premature infants may reach these milestones sooner than predicted by their corrected gestational age. From the age of 2 years to approximately 10 years, the growth rate is fairly constant at approximately 2.3 kg (5 pounds) each year. Growth velocity increases, and a major growth spurt occurs during adolescence. Height shows a growth pattern similar to that of weight; most infants increase their length by 50% in the first year, 100% in the first 4 years, and 300% by the age of 13 years. Changes in body composition accompany height and weight changes. Most notably, total body water decreases as adipose tissue increases. Total body water accounts for approximately 90% of total body weight at 24 weeks of gestation, 70% at term, and 60% by the age of 1 year.

Normal values for weight, length/height, and head circumference (until 3 years of age) in infants and children generally are expressed in terms of percentile-for-age; the reference standards most commonly used are WHO growth standards for infants and children younger than 2 years of age and the CDC growth charts developed by the National Center for Health Statistics (NCHS)

for children 2 years of age and older. As determined by CDC, the National Institutes of Health (NIH), and AAP, use of the WHO growth standards is recommended in the United States for patients younger than 2 years of age (https://www.cdc.gov/growthcharts/who_charts.htm). Three primary benefits of WHO growth standards for these patients cited as the reason for their use are establishing growth of the breastfed infant as the norm for growth, providing a better description of physiologic growth in infancy, and basing information on a high-quality study designed explicitly for creating growth charts. For children 2 years of age and older, the CDC growth charts should still be used, because the methods used to create both the CDC and WHO growth charts were similar for 2- to 5-year-olds, and WHO growth charts are based only on data for children up to 5 years of age.¹ Charts can be downloaded free of charge on the CDC website (www.cdc.gov/growthcharts). The infant charts are intended for use in term infants. In premature infants, growth parameters should be plotted on these charts using an age corrected for gestational age, as discussed previously, until the age of 18 months for weight, 40 months for length/height, and 18 months for head circumference.⁴ Charts for premature infants younger than 40 weeks' gestational age are available and should be used when appropriate. Specialized growth charts for children with certain pathologic conditions such as Down syndrome also are available. Although debate continues regarding the use of these charts versus standard charts for age, specialized growth charts may be helpful in assessing growth within these populations.^{5,6} Clinicians should be aware that limitations to the use of these charts exist and that not all children with a given condition may be accurately represented by the data presented. CDC provides information on the Down syndrome-specific growth charts on its website (<https://www.cdc.gov/ncbddd/birthdefects/downsyndrome/growth-charts.html>). The most commonly used charts for premature infants are the Fenton and Olsen charts (available at www.ucalgary.ca/fenton/2013chart and <https://www.aap.org/en-us/Documents/GrowthCurves.pdf>, respectively).

Most infants' growth parameters will fall between the 3rd and 97th percentiles on the gender-specific weight-for-age, length/height-for-age, weight-for-length, and head circumference-for-age charts. In children younger than 2 years of age, a recumbent length measurement is obtained in the primary care office, whereas in children 2 years of age or older, a standing height is measured. Most children grow along a percentile established shortly after birth, but spurts and plateaus are common. *Failure to thrive* was historically defined as a fall of 2 or more growth percentiles from a previously established

percentile in 6 months or less but now is defined as growth that is significantly lower than the norms for the affected child's age and gender.⁴ If growth is not progressing as expected, particularly in the first year of life, when growth should be rapid, the infant's diet and other potential contributory factors (e.g., environment, diseases, syndromes) should be evaluated. The four most commonly associated factors for failure to thrive are medical, nutritional, developmental, and social.⁴ Satisfactory growth is the most sensitive indicator of whether nutritional needs are being met.

For children 2 years and older, body mass index (BMI)-for-age charts can be useful in assessing obesity risk. BMI, a measure of body weight adjusted for height, is a useful tool to assess body fat. BMI is calculated as weight in kilograms divided by height in meters squared. The use of BMI was recommended by an expert committee consisting of members from the American Medical Association, the Health Resources and Services Administration and CDC (https://www.cdc.gov/healthyweight/assessing/bmi/childrens_bmi/about_childrens_bmi.html). The committee's nomenclature changes were intended to make it easier to discuss children's weight issues with parents and children and to affect the transition to adult assessments. According to these recommendations, a child whose BMI is at or above the 85th percentile but below the 95th percentile or 30 kg/m², whichever is smaller, should be classified as *overweight*. A child whose BMI is at or above the 95th percentile or 30 kg/m², whichever is smaller, should be classified as *obese*.⁷ In 2011–2012, 8.1% of infants and toddlers from birth to 2 years of age had BMIs at or above the 97th percentile on WHO growth charts, whereas 18.5% of children and adolescents 2–19 years of age in 2015–2016 had values at or above the 95th percentile on the CDC growth charts.^{8,9} The prevalence of obesity in children and adolescents 2–19 years of age has not statistically changed since 2013–2014 (17.2% in 2013–2014 versus 18.5% in 2015–2016) but still is higher than the *Healthy People 2020: National Health Promotion and Disease Prevention Objectives* goal of 14.5%.^{9,10} The incidence of obesity remains high. However, the proportion of obesity prevalence differs among various ethnic groups, with 25.8% of Hispanics, 22% of non-Hispanic Blacks, 14.1% of non-Hispanic Whites, and 11% of non-Hispanic Asians between 2 and 19 years of age classified as obese.⁹

A BMI below the 5th percentile is indicative of *underweight*. In applying these definitions, however, pharmacists and other health care providers should keep in mind that because of the way the growth charts were developed, values for

5% of normally growing and healthy children will fall below the 5th percentile and those for another 5% will fall above the 95th percentile on the weight-for-age or height-for-age charts. These children should not be branded as “malnourished” and “obese,” respectively.

Energy Requirements and Growth

Acceptable growth is achievable only with adequate intake, absorption, and utilization of energy, protein, carbohydrates, minerals, and vitamins. The Food and Nutrition Board of the National Research Council has established dietary reference intakes (DRIs) as reference values for nutrient intake sufficiency and safety. The DRIs for micronutrients are discussed in detail in [Chapter 23](#), and tables in that chapter list the current established recommended dietary allowances (RDAs) and adequate intakes (AIs) for healthy infants and children. [Table 26–2](#) lists the daily DRIs of macronutrients for healthy infants and children.¹¹ Children with various diseases and syndromes may have different needs. An example is the need for “catch-up” calories in infants and children recovering from failure to thrive. Calorie requirements for catch-up growth are often 1.25 times those of age-matched peers, depending on the degree of catch-up growth needed. The average rate of weight gain for corrected age for prematurely born infants is up to 2–3 times more.⁴ In patients with fat malabsorption (e.g., from cystic fibrosis or other cause of pancreatic insufficiency, bile acid deficiency, or short bowel syndrome), calories for catch-up growth may be 1.5 times or more those of age-matched peers.

Table 26–2 Daily Dietary Reference Intakes of Macronutrients for Full-Term Infants and Children^{a,b}

Nutrient	0–6Months	7–12Months	1–3Years	4–8Years	9–13Years
Energy ^c (kcal)	M: 570	M: 743	M: 1046	M: 1742	M: 2279
	F: 520	F: 676	F: 992	F: 1642	F: 2071
Protein ^c					
(g/kg)	1.5	1.2 ^d	1.1 ^d	0.95 ^d	0.95 ^d
(g)	9.1	13.5 ^d	13 ^d	19 ^d	34 ^d

Nutrient	0–6Months	7–12Months	1–3Years	4–8Years	9–13Years
Carbohydrate (g)	60	95	130 ^d	130 ^d	130 ^d
Water (L) ^e	0.7	0.8	1.3	1.7	M: 2.4
					F: 2.1
Fat (g)	31	30	ND	ND	ND
Alpha-linolenic acid (g)	0.5	0.5	0.7	0.9	M: 1.2
					F: 1
Linoleic acid (g)	4.4	4.6	7	10	M: 12
					F: 10
Fiber (g) ^f	ND	ND	14	M: 19.6	M: 25.2
				F: 16.8	F: 22.4

^a Expressed as AIs unless noted otherwise.

^b DRIs have not been established for premature infants.

^c Estimated requirements; include needs associated with growth (i.e., energy expenditure plus energy deposition). The assumed normal body weight and length used for the DRIs are as follows: 0–6 months: 6 kg, 62 cm; 7–12 months: 9 kg, 71 cm; 1–3 years: 12 kg, 86 cm; 4–8 years: 20 kg, 115 cm; and 9–13 years: 36 kg, 144 cm for males, 37 kg, 144 cm for females.

^d Expressed as RDA.

^e Water from all sources including formula, human milk, foods, beverages, and drinking water.

^f Fiber guidelines are provided for adolescents and include goals of 30.8 g for males 14–18 years of age and 25.2 g for females 14–18 years of age.

Key: AI = Adequate intake; DRI = dietary reference intake; F = female; M = male; ND = not determined; RDA = recommended dietary allowance.

Source: Reference 11; U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion. *2015–2020 Dietary Guidelines for Americans*. 8th ed.

December 2015. Available at: <https://health.gov/our-work/food-and-nutrition/2015-2020-dietary-guidelines/>. Accessed July 26, 2020.

Energy requirements vary with age and clinical condition. Total energy expenditure is a combination of basal energy needs: the energy required to digest food (thermic effect of feeding, also called “specific dynamic action of food”), thermoregulation, and activity. Estimates of energy requirements for infants and children are based on meeting total energy expenditure plus promoting growth. An infant’s energy requirement is higher in relation to body mass than that of an adult or older child because of the rapid growth experienced during infancy. Estimated energy requirements for term infants and children are shown in [Table 26–2](#).¹¹ Although no RDA has been established, premature infants require 110–130 kcal/kg/day for enteral nutrition before hospital discharge and 100–120 kcal/kg/day after discharge.¹² In some cases, as much as 120–150 kcal/kg/day or more is needed for adequate growth.

Infant Nutritional Standards

An amendment to the Food, Drug, and Cosmetic Act (Infant Formula Act of 1980, amended 1986) gives the U.S. Food and Drug Administration (FDA) the authority to revise nutrient levels for infant formulas, establish quality control, and require adequate labeling. FDA sets specifications for minimum amounts of 29 nutrients and maximum amounts of 9 of those nutrients. All formulas marketed in the United States must meet these requirements. Parents should be cautioned against using any infant formula not manufactured in the United States. FDA alerts have warned of the dangers of using infant formulas from China whose contents fall well below FDA standards. Formulas granted exemption from FDA-established nutrient specifications must be labeled for use in infants with specific indications, such as inborn errors of metabolism, low birth weight, or other, unusual medical problems or dietary needs. A list of exempt formulas can be obtained at the FDA website (www.fda.gov). In addition, FDA has published guidance documents to clarify certain requirements for industry on labeling of infant formula, including nutrient content claims, health claims, and qualified health claims, and requirements

for preparation directions and a statement regarding the need to add or not add water. The September 2016 guidance document is available at <http://www.fda.gov/FoodGuidances>.

Components of a Healthy Diet

Infants require the same dietary components as for adults: fluid, carbohydrates, proteins, fats, and micronutrients. However, the desired proportions of these components in the infant diet differ from those recommended for adults.

Fluid

Water is an important part of an infant's diet in that it makes up a larger proportion of the infant's body weight than that of older children or adults. The Holliday–Segar method is most often used to estimate maintenance water needs: 100 mL/kg/day for the first 10 kg of body weight, plus 50 mL/kg/day for each kilogram between 10 and 20 kg, and 20 mL/kg/day for each kilogram over 20 kg. Body surface area also may be used to estimate daily fluid requirements; fluid requirements are approximately 1500 mL/m²/day. These methods, however, will underestimate the needs of premature infants, whose requirements are in general much higher (i.e., 120–170 mL/kg/day, or as high as 200 mL/kg/day based on specific patient circumstances). Adequate water intake in the first 6 months of life can be derived from human milk or formula. Both contain sufficient amounts of water, so the normal, healthy infant does not need supplemental water. At the age of 6–12 months, when solid foods are introduced, water intake remains high, because most infant foods contain at least 60%–70% more water than other foods, and formula or human milk intake also should still be high.

Renal excretion, evaporation from the skin and lungs, and, to a lesser extent, elimination of feces are the major routes of fluid loss. Increased water loss caused by diarrhea, fever, or unusually rapid breathing, particularly in concert with decreased water intake, may result in significant dehydration and electrolyte imbalance and must be offset by fluid intake in excess of maintenance needs. (Refer to [Chapter 19](#) for information on the diagnosis and management of dehydration in pediatric patients.)

Carbohydrates

An AI for carbohydrates has been established for infants ([Table 26–2](#)).¹¹ Under normal circumstances, an infant can efficiently use a diet with 40%–50% of total calories from a carbohydrate source. Carbohydrate intake should be balanced with adequate fat intake to allow proper neurologic development. A carbohydrate-free diet generally is undesirable because it may lead to metabolic modifications favoring fatty acid breakdown, dehydration, and tissue protein and cation loss. However, children with seizure disorders may receive an essentially carbohydrate-free diet—the ketogenic diet—because these metabolic effects may facilitate seizure control. Use of a ketogenic diet should be under direct, strict medical supervision, with additional management as appropriate by a registered dietitian or other qualified health care provider.

Lactose, the primary carbohydrate source in human milk and most milk-based formulas, is hydrolyzed to its monosaccharide components, glucose and galactose, by gastric acid and the enzyme lactase. Congenital lactase deficiency is a rare type of lactose intolerance resulting from an inborn error of metabolism. Infants born prematurely, before the maturation of significant lactase activity (before approximately 36 weeks' gestational age), are relatively lactase-deficient. Secondary lactase deficiency is a temporary reduction in intestinal lactase caused by gastroenteritis or significant malnutrition. Because of low lactase activity, infants with congenital lactase deficiency, premature infants, and infants recovering from diarrhea or severe malnutrition may be unable to completely metabolize the lactose found in human milk or milk-based infant formulas, with consequent development of lactose intolerance resulting in diarrhea, abdominal pain or distention, bloating, gas, and cramping.

Fiber intake is of considerable interest, because in adults, high-fiber diets have been associated with the prevention of diverticular disease, colon cancer, and coronary heart disease. (See [Chapter 24](#) for further discussion of fiber.) AAP recommends following the Dietary Guidelines 2015–2020 for Americans from the U.S. Departments of Health and Human Services and Agriculture (<https://health.gov/dietaryguidelines/2015/resources/2015-2020-Dietary-Guidelines.pdf>). An AI for fiber for infants 0–12 months of age has not been established. Infants rarely require added fiber to maintain normal bowel function. Starting from the age of 6–12 months, however, whole cereals, green

vegetables, and legumes typically are introduced to provide a source of fiber in the infant's diet. The fiber AI for older children is shown in [Table 26–2](#). Adult values are reached by the teenage years.

Protein and Amino Acid

The most recent revision of the DRIs established new AIs for protein in term infants and children ([Table 26–2](#)).¹¹ Total body protein increases by an average of 3.5 g daily in the first 4 months of life and by 3.1 g daily over the next 8 months, representing an overall increase in body protein composition from 11% to 15% of total body weight.

A specific protein's amino acid composition (i.e., chemical makeup) also is important. Amino acids are classified as essential (or indispensable), nonessential, or conditionally essential. The amino acids cysteine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, tyrosine, and valine are considered essential for infants, because the human body cannot synthesize them from other amino acid and carbohydrate precursors. In the neonate and young infant, immature biochemical pathways for synthesis or conversion of select amino acids may prevent adequate synthesis for normal growth and development.

Taurine is an especially important amino acid in infancy. Quantities in human milk are high, and all infant formulas are supplemented during the manufacturing process to provide the same margin of physiologic safety as for human milk.¹³ Taurine is not an energy source and is not used for protein synthesis, but it serves as a cell membrane protector by attenuating toxic substances (e.g., oxidants, secondary bile acids, excess retinoids) and acting as an osmoregulator. Additionally, the conjugation of bile acids requires taurine. Taurine deficiency can result in reduced bile acid secretion, leading to accumulation of toxic bile acids, retinal dysfunction, slow development of auditory brainstem evoked response in preterm infants, and poor fat absorption in preterm infants and children with cystic fibrosis. Substantial clinical or physiologic improvement can be obtained with use of taurine supplements in these conditions.

Despite similar amino acid densities and milk intakes in formula-fed and human milk-fed infants, serum concentrations of some amino acids measured in formula-fed infants tend to exceed those measured in human milk-fed

infants; however, both groups exhibit comparable growth. The protein content of human milk evolves with the growing infant's needs, but the high protein requirements of preterm infants are not completely met by early human milk. Fortification with commercially available powders or liquids is required for the preterm infant to achieve reasonable amino acid profiles and to meet requirements for expected growth rates. In evaluating the adequacy of an infant's protein intake, it is important to consider not only the absolute amount of protein ingested but also the *linear growth velocity* (i.e., rate of linear growth over a defined period of time), the quantity of nonprotein calories and other nutrients necessary for protein synthesis, and the quality of the protein itself.

Fat and Essential Fatty Acids

Fat is the most calorically dense component in the diet, providing 9 kcal/g, compared with 4 kcal/g for both protein and carbohydrates. Fat accounts for approximately 50% of the nonprotein energy in both human milk and infant formula. Infant feeding choices, especially fat and calorie intake, are increasingly being linked to obesity and other diseases (e.g., diabetes, cardiovascular disease [CVD]) in adulthood. Despite these concerns, children younger than 2 years of age (the time of most rapid growth and development requiring high energy intakes) should not receive a fat- or cholesterol-restricted diet unless medically prescribed. Children between 12 months and 2 years of age who are at increased risk for subsequent early development of CVD because of a family history of obesity, dyslipidemia, or CVD may be candidates for reduced-fat milk products.¹⁴ AAP supports this position, with attention to appropriate fat intake, on account of the recognized need for adequate fatty acids for normal neurologic development and adequate calories for growth.¹⁴ Parents of children with or without hypercholesterolemia should be encouraged to adopt a diet that contains no more than 30% of total calories from fat, with 7%–10% of calories from saturated fats and dietary cholesterol (≤ 300 mg daily).¹⁴

The diet also must contain small amounts of the two essential polyunsaturated fatty acids (PUFAs): linolenic acid, an omega-3 (n-3) fatty acid, and linoleic acid, an omega-6 (n-6) fatty acid. These fatty acids are precursors for the n-3 and n-6 long-chain PUFAs—docosahexaenoic acid (DHA) and arachidonic acid (ARA), respectively. Essential fatty acid deficiency, rarely seen in the United States, can manifest as increased metabolic rate, failure to thrive, hair loss, dry flaky skin, thrombocytopenia, and impaired wound healing. Because of substantial

fat stores, overt clinical manifestations of essential fatty acid deficiency generally are delayed for weeks in older children and adults; however, rapid onset (within days) may occur in premature infants with inadequate linoleic acid in their diets. Linoleic acid represents the bulk of PUFAs in infant formulas. Generally, an intake of at least 10% of total calories from fat and linoleic acid equal to at least 2%–4% of total dietary calories is adequate to prevent essential fatty acid deficiency; 3%–7% is the amount found in human milk.¹⁵ Providers also should ensure an adequate provision of carnitine in at-risk patients. Carnitine is required for the transport of long-chain fatty acids across the mitochondrial membrane for oxidation. Preterm infants are at risk for carnitine deficiency, because its accrual from the mother occurs late, during the third trimester. AIs for the essential PUFAs are shown in [Table 26-2](#).¹¹

Historically, infant formulas contained only the precursor PUFAs: linoleic and linolenic acid. Nowadays, most infant formulas are supplemented during manufacturing with DHA and ARA. In fact, more than 60 countries permit the addition of these fatty acids to infant formulas. AAP has not taken an official stand on whether infant formulas should be supplemented with DHA and ARA. However, the current European recommendations supported by the World Association of Perinatal Medicine, the Early Nutrition Academy, and the Child Health Foundation are for the addition of 0.2%–0.5% DHA to all infant formulas.¹⁶ These long-chain PUFAs, which are abundant in human milk but not in cow milk, are not considered essential but are thought to provide extra nutritional benefits. Increased amounts of DHA beyond what is currently being added to term infant formulas to mimic term human milk levels are being recommended for some preterm infants.^{17,18} DHA is important in both brain and eye development; a direct role for ARA is less clear. However, supplementation of DHA without ARA may lead to ARA deficiency and possible growth suppression.¹⁹

Whether the addition of DHA and ARA to infant formulas improves visual and cognitive function remains controversial. Some studies have shown benefit for visual function, cognitive and behavioral development, and growth with DHA and ARA supplementation in infants; other studies have shown no differences in supplemented versus control infants.²⁰⁻²² Benefits such as a decreased prevalence of allergies and a reduced incidence of common respiratory illnesses also have been suggested, but studies have had mixed results.²³⁻²⁵ No adverse effects have been noted in infants receiving DHA- and ARA-supplemented formulas; however, two studies in which the formula was

supplemented with only DHA reported growth suppression, stressing the importance of supplementation with both DHA and ARA.²² Several studies have examined the long-term benefits, particularly cognitive, of DHA supplementation and have not found sustained effects.^{26,27} However, significant benefits were observed in selected cognitive components in a more recent study conducted in children 3–6 years of age.²⁸

FDA has issued a “generally recognized as safe” (GRAS) notification to Martek Biosciences Corporation for its patented plant-based fatty acid blends DHASCO (DHA-rich single cell oil), extracted from *Cryptothecodinium cohnii*, and ARASCO (ARA-rich single cell oil), extracted from *Mortierella alpina*, both of which are currently used to supplement infant formulas during manufacturing.

Some evidence also indicates that maternal diet can affect fatty acid concentrations in the infant, both in utero and during lactation for human milk-fed infants, but supplementation has not been shown to significantly improve neurodevelopmental outcomes, visual acuity, or growth and only weakly favors supplementation.²⁹ Many prenatal vitamins, as both prescription (e.g., Nexa Plus, Duet DHA Balanced) and nonprescription (e.g., Similac Prenatal Vitamin, various store brands) products, currently are available, with an additional softgel capsule containing either DHA or DHA with eicosapentaenoic acid (EPA). The sources of DHA and EPA range from fish-based products to plant-derived sources. Enfamil Expecta Prenatal Dietary Supplement, softgel capsules containing 200 mg DHA, is marketed as a non-fish-based (algae) supplement for pregnant and lactating women to increase maternal dietary DHA and potentially increase DHA concentrations in their infants. These capsules may have less aftertaste than other sources of DHA. Additionally, selecting “burpless” products and freezing the product before administration may help to decrease the aftertaste of the fish-derived products. Routine supplementation during pregnancy and lactation remains controversial and should be discussed with a knowledgeable health care provider.

Micronutrients

DRIs for term infants (given as RDAs if defined or as AIs if RDAs are not defined) for vitamins and minerals, including trace elements, are shown in Tables 23–3 and 23–4 in [Chapter 23](#). Precise needs are difficult to define and

depend on energy, protein, and fat intakes as well as absorption and nutrient stores. Infant formulas are supplemented with adequate amounts of vitamins and minerals to meet the needs of most term and premature infants when the appropriate formula is chosen. As with protein fortification, human milk must be fortified to meet the micronutrient needs of most premature infants. Appropriate supplementation is included in the discussion of specific milks and formulas.

Infant Food Sources

Human milk– and cow milk–based formulas are the primary food sources for most infants in the United States. Soy protein–based formulas and goat milk are alternatives. A variety of formulas are available to feed infants with special nutritional needs, including those unable to consume a regular oral diet, those with inborn errors of metabolism, and those with various malabsorptive conditions. Most infants and children receive either human milk or an enteral formula by mouth; however, some children will receive nutrition through feeding tubes such as naso- or orogastric, nasoduodenal, gastrostomy, or jejunostomy tubes. A discussion of these feeding techniques is beyond the scope of this chapter. More information on enteral feeding tubes and potential complications is available on the following websites: www.nutritioncare.org and www.oley.org.

Human Milk

Both WHO and AAP recommend that infants be breastfed without supplemental foods or liquids for approximately the first 6 months (i.e., exclusive breastfeeding) and be encouraged to breastfeed for the first year of life or longer if desired by mother and child.^{30–32} Breastfeeding initiation rates worldwide have increased steadily since 1990, with the rate at hospital discharge increasing from a low of 24.7% in 1971 to 83.2% in 2015. However, in 2015, the reported rates of any breastfeeding in infants 6 and 12 months of age were only 57.6% and 35.9%, respectively. Sociodemographic factors affect breastfeeding rates. Black women are less likely than White, Hispanic, and Asian women to breastfeed. Poor, unmarried, and poorly educated women also are less likely to breastfeed their infants. [Table 26–3a](#) shows breastfeeding rates in the United States for infants born in 2015 based on various ethnicities.^{33–35}

Table 26–3 Breastfeeding Rates in the United States, 2015

a. Ethnicity-Based					
	All Ethnic Groups (%)	Asian (%)	Black (%)	Hispanic (%)	White (%)
Breastfeeding at					
Any time after birth	83.2	89.3	69.4	84.6	85.9
6 months	57.6	72.2	44.7	54.1	62
12 months	35.9	50.3	24	32.6	39.8
b. Compared With Healthy People 2020 Goals					
	Healthy People 2020 Goal (%)	Observed Rate (%)			
Breastfeeding at					
Birth	82	83.2			
6 months	61	57.6			
1 year	34	35.9			
Exclusive breastfeeding at					
3 months	46	46.9			
6 months	25	24.9			
Formula supplementation within first 2 days of life	14	17.2			

Source: [References 10, 33, and 34.](#)

Because breastfeeding is a major public health issue, breastfeeding goals were included in *Healthy People 2020: National Health Promotion and Disease Prevention Objectives*, the national plan to improve the health of the American people.¹⁰ Objectives of *Healthy People 2020* are provided in [Table 26–3b](#),

including data from 2015 (the year of last official reporting of information). All values showed improvement from the 2006 baseline levels, and goals were met for any breastfeeding at birth, any breastfeeding at 1 year, and exclusive breastfeeding at 3 months. The proposed breastfeeding goal for *Healthy People 2030* will involve only exclusive breastfeeding at 6 months, which aligns with the recommendations of WHO and CDC (www.healthypeople.gov). AAP recommends support for breastfeeding through the first year of life. The AAP policy statement on breastfeeding and the use of human milk was updated in 2012 and includes reinforcement of breastfeeding and human milk as the reference normative standards for infant feeding and nutrition and reaffirmation of the recommendation for exclusive breastfeeding for 6 months, followed by continued breastfeeding for 1 year or longer as mutually desired by mother and infant. AAP cautions that medical contraindications to breastfeeding are rare in the United States (e.g., positive maternal human immunodeficiency virus [HIV] serostatus, active tuberculosis without at least 2 weeks of prior treatment, infant galactosemia, or need for maternal medication not compatible with breastfeeding).³⁶ Moreover, AAP recommends (1) the use of WHO growth charts to avoid mislabeling of infants as underweight and with failure-to-thrive status, (2) hospital initiatives to encourage and support the initiation and sustaining of exclusive breastfeeding, (3) support by pediatricians as advocates of breastfeeding, and (4) acknowledgment of the economic benefits to society of breastfeeding.³¹

Breastfeeding not only offers an optimal source of nutrition for the infant but also provides other benefits, such as improved mother–child bonding and advantages for the infant’s general health, growth, and development. Strong evidence indicates that a human milk–based diet decreases the incidence and severity of various infections (e.g., nonspecific gastrointestinal tract infections, respiratory tract infections, otitis media) in infants and necrotizing enterocolitis in premature infants.³⁰ Other proposed benefits of human milk include decreased rates of sudden infant death syndrome, type 1 and type 2 diabetes, leukemia, overweight, obesity, hypercholesterolemia, asthma, atopic dermatitis, eczema, celiac disease, and childhood inflammatory bowel disease. Breastfeeding also has been associated with slightly enhanced performance on tests of cognitive development; however, the effect of genetic and socioenvironmental factors on intelligence is difficult to measure separately from that of breastfeeding.³¹ Among premature infants, improvement also is seen in clinical feeding tolerance, quicker attainment of full enteral feeding, and more favorable neurodevelopmental outcomes. With recognition of these

benefits, AAP recommends use of human milk for all preterm infants. If the mother's own milk cannot be provided, pasteurized donor milk, term or preterm as appropriate, should be used.³¹

Besides enhanced mother–child bonding, maternal benefits of breastfeeding include decreased postpartum bleeding, more rapid uterine involution, decreased menstrual blood loss, increased spacing between children, earlier return to prepregnancy weight, decreased risk of breast and ovarian cancer, decreased risk of rheumatoid arthritis, and decreased rates of hip fracture and osteoporosis in the postmenopausal period.

A savings of more than \$13 billion per year (\$3.7 billion in direct and indirect pediatric health costs, with \$10.1 billion in premature death from pediatric diseases) could be realized if 90% of mothers in the United States would exclusively breastfeed for 6 months. If only 80% chose to exclusively breastfeed for 6 months, \$10.5 billion per year would be saved. More important, 911 deaths annually would be prevented if a 90% exclusive breastfeeding rate was achieved (741 deaths with an 80% achievement rate).^{37,38} In the business environment, the case for breastfeeding is an economic one. For every \$1 a business spends on creating and supporting lactation support programs at the worksite, a \$2–\$3 return on investment is achieved.³⁹ An economic analysis of estimated direct health care costs for diarrhea, lower respiratory tract infections, and otitis media in the first year of life found that costs for infants who were never breastfed were \$300 more than for infants exclusively breastfed for at least 3 months.⁴⁰

Many unanswered questions regarding the protective effects of breastfeeding remain: What is the duration of such protection after breastfeeding has been discontinued? What influence does maternal age have on the protective effect? How great is the interactive effect of social and demographic variables? How does the addition of solid foods (complementary feeding) to the diet of a human milk–fed infant influence the protective effect? What consequence does partial formula feeding have for the protective effect? Well-designed studies are needed to answer these questions.

The impact of the use of breast pumps also should be considered. The 2005–2007 Infant Feeding Practices Study II (IFPS II) assessed the use of expressed human milk among breastfeeding mothers of infants 1.5–4.5 months of age.⁴¹ Of these mothers, 85% had expressed their own milk some time during their child's infancy, and 5.6% of mothers had exclusively fed their

infants expressed human milk. As with breastfeeding rates in general, the use of expressed human milk is more common among women with a higher level of education and a higher household income. The primary reason reported in IFPS II for the use of expressed human milk is the ability to have someone else feed the infant, allowing many mothers to continue to provide breast milk while working outside of the home. Unfortunately, the use of expressed human milk is not always an elective decision. When women express milk for nonelective reasons (i.e., to alleviate sore nipples, to increase milk supply, or to allow later feedings when the baby is unable to nurse owing to sickness or when the mother is working), a concern is that breastfeeding duration may be adversely affected. Mothers thought to be less likely to continue to breastfeed, with consequent shorter duration of human milk feedings for their infants, include those who are pumping because of either employment or a recognized difficulty with infant feeding at the breast.⁴²

Although breast milk pumping can provide many of the same benefits to infant and mother, some potential problems have been noted. If an electric breast pump is used improperly, the mother can incur mastitis, pain, trauma, and nipple wounds. With respect to the infant, the expressed milk can become contaminated with bacteria if it is expressed or stored improperly.⁴³

Recommendations and protocols for handling and storing human milk have been established by CDC and the Academy of Breastfeeding Medicine.^{44,45}

Storage of human milk in nonglass containers is associated with destruction of some key milk components, and storing milk at either refrigerator or freezer temperatures can reduce levels of key milk components (i.e., vitamin C, lipids, and immunologic cells). Finally, the composition of human milk changes throughout a single feeding and with the infant's age. For example, most mothers who pump their milk breastfeed the infant first and then express the remainder for later use. This method separates the foremilk, which is high in carbohydrate content, from the hindmilk, which is high in fat content. Such separation of the macronutrient components within a feeding of mother's milk can lead to adverse GI effects in the infant, such as diarrhea. Well-designed research is needed in this area to assess the true impact of the use of breast pumps on maternal health and infant nutrition.⁴¹

Very few contraindications to the use of human breast milk have been recognized. In developed countries, such as the United States, one reason for not breastfeeding is a maternal diagnosis of HIV infection, which can be transmitted through human milk. Women with HIV-seropositive status in

underdeveloped countries, however, are encouraged to breastfeed, because the risk of infant morbidity and death with formula use (from inadequate sanitation or refrigeration and illiteracy-associated errors in preparation) is greater than the risk of HIV transmission.³¹ Other reasons for not breastfeeding in women in developed countries, either temporarily or permanently, include the following medical disorders and conditions: classic galactosemia in the infant, active maternal untreated tuberculosis, maternal human T cell lymphotropic virus type I or II infection, presence of a herpes simplex lesion on the breast (although use of the other breast may be possible), and the maternal use of drugs not compatible with breastfeeding. Several excellent textbooks provide information regarding the use of drugs during lactation and pregnancy (e.g., Briggs' *Drugs in Pregnancy and Lactation*, Hale's *Medications & Mother's Milk*; see also the Preface of this book for a detailed explanation of the pregnancy data).

In addition, a comprehensive database of available information on drugs in lactation (LactMed) is maintained by the National Library of Medicine (<http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>) and is currently recommended as a definitive source by AAP.⁴⁶ Further questions can be directed to the poison control center hotline (800-222-1222) or the National Breastfeeding Helpline (800-994-9662) or website (<http://www.womenshealth.gov/breastfeeding/>).

The overall risk of an adverse reaction to a drug in a breastfed infant depends on the concentration in the infant's blood and the effects of the drug on the infant (<http://www.infantrisk.com/content/drug-entry-human-milk>). Feeding immediately before the mother's dose may help minimize exposure, because the concentration in milk is likely to be lowest toward the end of the dosing interval. This may not be the case with lipid-soluble drugs. Alternating breast and bottle feedings or discarding the pumped breast milk during drug therapy is an option if the need for a particular drug is short term.

In the United States and other countries, human milk donor banks have been established, with 28 member banks in the Human Milk Banking Association of North America (HMBANA). Another source of human donor milk is preparations available from private companies such as Prolacta Bioscience: Human milk from carefully screened donors undergoes Holder pasteurization to eliminate potential viral and bacterial contaminants while maintaining most of the milk's unique immunologic factors.^{47,48} An estimated 20%–62% of the

immunoglobulin A (IgA) is lost in processing;⁴⁹ however, because cow milk contains no IgA at all, infants who receive donor human milk still benefit from its presence at lower levels. The cost is approximately \$4 per ounce plus shipping and handling. More information about donor milk banks, including how to be a donor or to receive donor milk, can be obtained on the HMBANA and Prolacta websites (www.hmbana.org and www.prolacta.com, respectively). A positive impact on decreased rates of necrotizing enterocolitis, a severe inflammation of the intestinal mucosa, with the use of donor milk when maternal human milk is either unavailable or insufficient has been shown for very low-birth-weight infants.⁵⁰

Cow Milk

Cow milk is the primary nutrient source for commercially prepared milk-based infant formulas. In both human milk and cow milk, more than 200 constituent factors have been identified in the fat- and water-soluble fractions. Estimates of the major nutrients contained in pooled mature human milk, preterm human milk, and whole cow milk are listed in [Table 26–4](#).

Table 26–4 Average Composition of Mature Human Milk, Preterm Milk, and Whole Cow Milk

Component	Mature Human Milk ^a	Preterm Milk	Whole Cow Milk
Water (mL/100 mL)	87.1	–	87.2
Energy			
(kcal/100 mL)	65–70	67	66–68
(kcal/oz)	19.5–21	20	19–20
Protein (g/100 mL)	0.9	1.41	3.3–3.4
Whey/casein ratio	55:45	–	18:82
Alpha-lactalbumin (g/100 mL)	0.326	–	0.1
Alpha-lactoglobulin (g/100 mL)	–	–	0.4
Lactoferrin (g/100 mL)	0.194	–	Trace
Secretory IgA (g/100 mL)	0.1	–	Trace
Albumin (g/100 mL)	0.04	–	0.04

Component	Mature Human Milk ^a	Preterm Milk	Whole Cow Milk
Fat (g/100 mL)	3.9	3.89	3.4–3.8
Carbohydrate (g/100 mL)	6.7–7.2 ^b	6.6	4.7–4.8 ^c
Minerals			
Calcium (mg/L)	200–250	250	1200
Phosphorus (mg/L)	120–140	130	960
Calcium/phosphorus ratio	2:1	~2:1	1.3:1
Sodium (mg/L)	120–250	250	500
Potassium (mg/L)	400–550	570	1560
Chloride (mg/L)	400–450	550	1020
Magnesium (mg/L)	30–35	31	120
Vitamins			
Vitamin A (IU/L)	1333–3000 ^d	3900	1000
Thiamin (mcg/L)	200	210	300
Riboflavin (mcg/L)	400–600	480	1750
Niacin (mg/L)	1.8–6	1.5	0.8
Pyridoxine (mg/L)	0.09–0.31	0.15	0.5
Pantothenate (mg/L)	2–2.5	1.81	3.6
Folic acid (mcg/L)	80–140	33	50
Biotin (mcg/L)	5–9	–	35
Vitamin B ₁₂ (mcg/L)	0.5–1	0.5	4
Vitamin C (mg/L)	100	107	17
Vitamin D (IU/L)	13.2	20	24
Vitamin E (IU/L)	0.0045–0.012	11	0.4–0.9
Vitamin K (mcg/L)	2–3	2	5

Component	Mature Human Milk ^a	Preterm Milk	Whole Cow Milk
Trace Minerals			
Chromium (mcg/L)	45–55	–	20
Manganese (mcg/L)	3	60	20–40
Copper (mg/L)	0.2–0.4	0.64	100
Zinc (mg/L)	1–3	3.4	3.5
Iodine (mcg/L)	150	–	80
Selenium (mcg/L)	7–33	–	5–50
Iron (mg/L)	0.3–0.9	1.2	0.46
Fluoride (mcg/L)	4–15	–	–

^a ≥28 days post partum.

^b As lactose, glucose, and oligosaccharides.

^c As lactose.

^d As both retinol and carotenoids.

Key: IgA = Immunoglobulin A; IU = international units.

Source: Picciano MF. Representative values for constituents of human milk. In: Schanler RJ, ed. Breastfeeding 2001, part 1: the evidence for breastfeeding. *Pediatr Clin North Am.* 2001;48:263–4; Meeting the specific needs of low birth weight and premature infants in the hospital (A8100). Columbus, Ohio: Abbott Nutrition: Abbott Laboratories, 1998:56; and Committee on Nutrition, American Academy of Pediatrics. Appendix R. In: Kleinman RE, Greer FR, eds. *Pediatric Nutrition*. 7th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2014:42, 1431–1432.

Whole Cow Milk

Whole cow milk is not suitable for providing nutrition to infants younger than 1 year. Because of the low concentration and poor bioavailability of iron, a whole cow milk–based diet has been associated with iron-deficiency anemia.^{51,52}

Sensitivity to dietary proteins, most commonly cow or soy milk proteins, can manifest as occult GI bleeding, further increasing the risk of anemia. In the past decade, convincing evidence has accumulated to indicate that iron deficiency impairs psychomotor development and cognitive function in infants, even those with relatively mild anemia. Milk protein intolerance and/or allergy also can result in rash, wheezing, diarrhea, vomiting, colic, and anaphylaxis when whole cow milk is used. Moreover, when whole cow milk is fed with solid food, infants receive unnecessarily high intakes of protein and electrolytes, resulting in a high renal solute load (RSL)⁵³ (Table 26–5). The implications of a high RSL are discussed later in the chapter. The current position of the AAP Committee on Nutrition (AAP-CON) is that iron-fortified infant formula is the only acceptable alternative to human milk. The use of cow milk is not recommended during the first year of life.⁵⁴

Table 26–5 Potential Renal Solute Load (PRSL) for Selected Milks and Infant Formulas

Milk/Formula	PRSL	
	mOsm/L	mOsm/100 kcal
Human milk	93	14
Milk-based formula	135–260	20–39
Soy protein-based formula	160	24
Whole cow milk	308	46
Skim cow milk	326	93
FDA upper limit	277	41
Beikost ^a	153	23

^a *Beikost* is foods other than milk or formula.

Key: FDA = U.S. Food and Drug Administration.

Source: Reference 53.

Reduced-Fat Cow Milk

Consumption of reduced-fat cow milk, such as skim milk (0.1% fat), low-fat milk (1% fat), and reduced-fat milk (2% fat), has been advocated to prevent obesity and atherosclerosis as part of a “heart-healthy diet.” However, when the low-fat diet recommended for adults is imposed on children younger than 2 years of age, it puts them at risk for failure to thrive and impaired neurologic development. Infants who receive a major percentage of their caloric intake from reduced-fat milk may receive an exceedingly high protein intake and an inadequate intake of essential fatty acids. The maximum protein concentration allowed by FDA in infant formulas is 4.5 g/100 kcal, but skim milk and 2% milk provide approximately 8–10 g/100 kcal and 7–10 g/100 kcal, respectively. Therefore, using reduced-fat cow milk for infant nutrition will provide an unbalanced percentage of calories supplied from protein, fat, and carbohydrates.

Per unit volume, skim milk has a slightly higher potential RSL (PRSL) than that of whole cow milk ([Table 26–5](#)). The solute concentration is further increased by water loss during processing. Reduced-fat milk is not recommended during episodes of diarrhea because of the possibility of hypertonic dehydration. As stated earlier, AAP does not recommend the use of low-fat diets during the first 2 years of life, except in children between 12 months and 2 years of age with a family history of CVD.

Evaporated Milk

Evaporated milk is a sterile, convenient source of cow milk with standardized concentrations of protein, fat, and carbohydrate. However, it is not recommended for infant feeding.

Goat Milk

Although goat milk is the primary milk source for more than 50% of the world’s population, it is rarely used in the United States for infants with intolerance to cow milk. Goat milk is commercially available in powdered and evaporated forms. It contains primarily medium- and short-chain fatty acids, so the fat is more readily digested than that in cow milk. The use of unfortified goat milk is not recommended by AAP, because it is deficient in folate and low in iron and vitamin D.⁵⁵ The evaporated and powdered whole milk forms of Meiyenber

goat milk, however, are supplemented with vitamin D and folic acid. Because goat milk is not a complete formula, vitamin supplementation is required if it is used for infant nutrition.

Commercial Infant Formulas

When provision of human milk to an infant is not possible (e.g., with lack of maternal supply, positive maternal HIV serostatus, or need for maternal medication contraindicated with breastfeeding) or not desired by the mother, then commercially supplied infant formulas constitute an acceptable alternative (Table 26–6). Differences in palatability, digestibility, sources of nutrients, convenience of administration, and cost among these formulas allow individualization for the infant’s special nutrient needs and the family’s resources.

Table 26–6 Selected Formulas for Infants and Children					
Table 26–6 Selected Formulas for Infants and Children					
Trade Name [form] (Mfr)	Energy ^a (kcal/ oz)	Protein ^a (g/ L)(C:W ratio)	Protein Source(s)	Carbohydrate ^a (g/ L)	Carbohydrate Source(s)
Infant Formulas					
Milk-Based Formulas					
Milk-Based Formulas					
Enfamil Premium Infant ^b [C,P,R] Enfamil Premium Infant ^b [C,P,R] (MJ)	20 20	13.5 (40:60) 13.5 (40:60)	Nonfat milk, whey protein concentrate Nonfat milk, whey protein concentrate	76 76	Lactose, galactooligosaccharide Lactose, galactooligosaccharide, polydextrose
Enfamil Gentlease ^c [P,R] Enfamil Gentlease ^c [P,R] (MJ)	20 20	15.6 (40:60) 15.6 (40:60)	Partially hydrolyzed nonfat milk and whey protein concentrate (soy) concentrate	73 73	Corn syrup solids [P] rice starch [P] Corn syrup solids [P] rice starch [R]
Gerber Good Start Gentle ^{d,e} Gerber Good [P] (G)	20	15.4 (8:100)	(soy) 100% whey protein partially	74.7	Lactose (70%), corn maltodextrin (30%), Lactose (70%), corn galacto-

Trade Name [form] (Mfr)	Energy Content ^a (kcal/ oz)	Protein ^a (g/ L) (C:W ratio)	Protein Source(s)	Carbohydrate ^a (g/ L)	Carbohydrate Source(s)
Start Gentle ^{d,e} [P] (G)			hydrolyzed partially (milk) hydrolyzed concentrate (milk)		maltodextrin (33%), galacto- oligosaccharides
Gerber Good Start Soothe [P] (G)	20	15.4 (0:100)	100% whey protein	74.7	Corn maltodextrin, galacto- oligosaccharides
Gerber Good Start Soothe [P] (G)	20	15.4 (0:100)	100% whey protein hydrolyzed partially (milk) hydrolyzed concentrate (milk)	74.7	Corn maltodextrin, galacto- oligosaccharides
Gerber Natura Organic Infant Formula with Iron [P] (G)	20	13.8 (0:100)	Organic nonfat milk, Organic whey protein milk, concentrate	80	Organic lactose, organic maltodextrin, organic galacto-oligosaccharides
Gerber Natura Organic Infant Formula with Iron [P] (G)	20	13.8 (0:100)	Organic whey protein milk, concentrate	80	Organic lactose, organic maltodextrin, organic galacto-oligosaccharides
Similac Advance ^{f,g} [C,P,R] (A)	19/20	13.3/14	Nonfat milk, whey protein concentrate	69.2/72.4	Lactose, galacto- oligosaccharides
Similac Advance ^{f,g} [C,P,R] (A)	19/20	13.3/14	Nonfat milk, whey protein concentrate	69.2/72.4	Lactose, galacto- oligosaccharides
Similac Advance Organic [P,R] (A)	20	14	Organic nonfat milk	73.7	Organic maltodextrin, organic sugar, fructose, oligosaccharides
Similac Advance Organic [P,R] (A)	20	14	Organic nonfat milk	73.7	Organic maltodextrin, organic sugar, fructose, oligosaccharides

Trade Name [form] (Mfr)	Energy Content ^a (kcal/ oz)	Protein ^a (g/ L) (C:W ratio)	Protein Source(s)	Carbohydrate ^a (g/ L)	Carbohydrate Source(s)
Soy Protein–Based Therapeutic Formulas					
Soy Protein–Based Therapeutic Formulas					
Enfamil ProSobee [C,P,R] (MJ)	20	16.9	Soy protein isolate, L- methionine, taurine, L- carnitine	72	Corn syrup solids
Enfamil ProSobee [C,P,R] (MJ)	20	16.9		72	Corn syrup solids
Gerber Good Start Soy ^e [C,P,R] (G)	20	16.9	Enzymatically hydrolyzed soy protein isolate, L- methionine, taurine, L- carnitine	75.1	Corn maltodextrin (sucrose (21%))
Gerber Good Start Soy ^e [C,P,R] (G)	20	16.9		75.1	Corn maltodextrin (sucrose (21%))
Similac Soy Isomil ⁹ [C,P,R] (A)	19/20	15.8/16.6	Soy protein isolate, L- methionine	67/69.7	Corn syrup solids, sucrose, fructo-oligosaccharides
Similac Soy Isomil ⁹ [C,P,R] (A)	19/20	15.8/16.6		67/69.7	Corn syrup solids, sucrose, fructo-oligosaccharides
Similac for Diarrhea [R] (A)	20	18	Soy protein isolate, L- methionine	68.3 [6 g/L of dietary fiber (soy)]	Corn syrup, sugar, sucrose, fructo-oligosaccharides, polydextrose
Similac for Diarrhea [R] (A)		18		68.3 [6 g/L of dietary fiber (soy)]	Corn syrup, sugar, sucrose, fructo-oligosaccharides, polydextrose
Other Therapeutic Infant Formulas					
Other Therapeutic Infant Formulas					Rice starch, lactose, maltodextrin, galactooligosaccharides, polydextrose
Enfamil A.R. [P,R] (MJ)	20 (80:20)	16.9	Nonfat milk	76	Enfamil A.R. [P,R] (MJ)
Enfamil A.R. [P,R] (MJ)	20 (80:20)	16.9	Nonfat milk	76	Enfamil A.R. [P,R] (MJ)
Similac Sensitive ^f	19(20 as [C])/19	13.5	Milk protein	71.4 (75.1) ^f /70.7	Corn syrup, modified rice starch, sucrose, fructo-oligosaccharides, polydextrose

Trade Name [form] (Mfr)	Energy Content ^a (kcal/ oz)	Protein ^a (g/ L) (C:W ratio)	Protein Source(s)	Carbohydrate ^a (g/ L)	Carbohydrate Source(s)
[C,P,R]/Similac For Spit Up ^f [P,R] (A)	(depending on formulation)	(14.5) ^f /13.8	isolate		rice starch, sugar, galacto- oligosaccharides
Similac Sensitive ^f [C,P,R]/Similac Sensitive ^f [P,R] (A)	19(20 as [C])/19 (depending on formulation)	13.5 (14.5) ^f /13.8	Milk protein isolate	71.4 (75.1) ^f /70.7	Corn syrup, modified rice starch, sugar, galactose
Similac Comfort ^f [P,R] (A)	19	14.9	Whey protein hydrolysate	70.7	Corn syrup solids, sugar, galactose, oligosaccharides
Similar Total Comfort ^f [P,R] (A)	19	14.9	Whey protein hydrolysate	70.7	Corn syrup solids, sugar, galactose, oligosaccharides
Similac PM 60/ 40 [P] (A)	20	15 (40:60)	caseinate, sodium caseinate	69	Lactose
Similac PM 60/ 40 [P] (A)	20	15 (40:60)	Whey protein caseinate, sodium hydrolysate caseinate (milk), L-	69	Lactose
Nutramigen ^h [C,R] (MJ)	20	18.9	cystine, L- cysteine, L- hydrolysate, L- (milk), L-	70	Corn syrup solids, modified corn starch
Nutramigen ^h [C,R] (MJ)	20	18.9	cystine, L- tyrosine, L-	70	Corn syrup solids, modified corn starch
Pregestimil			tryptophan, L- Casein carnitine, hydrolysate taurine (milk), L-		
[P,R]/Pregestimil 24 [R] (MJ)	20/24	18.9/23	cystine, L- cysteine, L- hydrolysate, (milk), L-	69/83	Corn syrup solids, modified corn starch
Pregestimil [P,R]/Pregestimil 24 [R] (MJ)	20/24	18.9/23	cystine, L- cysteine, L- tyrosine, L-	69/83	Corn syrup solids, modified corn starch
Similac Alimentum [P,R] (A)	20	18.6	tryptophan, taurine, L- Casein hydrolysate,	69	P: Corn maltodextrin modified corn starch
Similac Alimentum [P,R] (A)	20	18.6	L-cystine,L- Casein tyrosine,L- hydrolysate, tryptophan L-cystine,L-	69	P: Corn maltodextrin modified corn starch
			tyrosine,L- tryptophan		
PurAmino [P]	20	18.9	Free L-amino	72	Corn syrup solids,

Trade Name [form] (Mfr)	Energy Content ^a (kcal/ oz)	Protein ^a (g/ L) (C:W ratio)	Protein Source(s)	Carbohydrate ^a (g/ L)	Carbohydrate Source(s)
(MJ)			acids		modified tapioca st
PurAmino [P] (MJ)	20	18.9	Free L-amino acids	72	Corn syrup solids, modified tapioca st
Gerber Extensive HA ^{d,e,i} [P] (A)	20	17.6	100% whey, extensively hydrolyzed	73.7	Corn maltodextrin (90%), potato starch (10%)
Gerber Extensive HA ^{d,e,i} [P] (A)	20	17.6	100% whey, extensively hydrolyzed	73.7	Corn maltodextrin (90%), potato starch (10%)
EleCare (for Infants) [P] (A)	20	21	Free amino acids	72.3	Corn syrup solids
EleCare (for Infants) [P] (A)	20	18.7	Free L-amino acids	72/75.4 (6.3 g/L soluble fiber)	Corn syrup solids; Corn syrup solids; fructo-oligosacchar insulin (Syneo only)
Syneo Infant (Nut)					
Neocate Infant DHA&ARA [P]/Neocate	20	18.7	Free L-amino acids	72/75.4 (6.3 g/L soluble fiber)	Corn syrup solids; fructo-oligosacchar insulin (Syneo only)
Syneo Infant Enfaport [R] (MJ) (Nut)	30 (40:60)	36	Nonfat milk, whey protein concentrate	102	Corn syrup solids
Enfaport [R] (MJ)	30 (40:60)	36			
RCF ^{j,k} [C] (A)	20	20.3	Soy protein isolate, L- methionine, concentrate taurine, L- carnitine	102 68.3	Corn syrup solids None in actual prod
RCF ^{j,k} [C] (A)	20	20.3	Soy protein isolate, L- methionine, concentrate taurine, L- carnitine	68.3 89.4	None in actual prod
3232A ^{j,l} [P] (MJ)	20	18.7	hydrolysates (milk), L-L- cysteine		Modified tapioca st
3232A ^{j,l} [P] (MJ)	20	18.7	Casein, hydrolysates	89.4	Modified tapioca st
			L-tryptophan,		

Trade Name [form] (Mfr)	Energy Content ^a (kcal/ oz)	Protein ^a (g/ L) (C:W ratio)	Protein Source(s)	Carbohydrate ^a (g/ L)	Carbohydrate Source(s)
			(milk), L-tyrosine, L-tryptophan,		
Formulas for Premature Infants: Initial Feeding			L-tyrosine,		
Enfamil Premature 20 Cal [R] (MJ)	20	22 (20:80)	L-tryptophan, Nonfat milk, whey protein concentrate	73	Corn syrup solids, lactose
Formulas for Premature Infants: Initial Feeding					
Similac Special Care 20 with Iron Enfamil [R] (A)	20	20.3	Nonfat milk, whey protein concentrate	69.7	Corn syrup solids, lactose
Premature 20 Cal [R] (MJ)	20	22 (20:80)	Nonfat milk, whey protein concentrate	73	Corn syrup solids, lactose
Enfamil Premature 24 Cal [R]/Enfamil Similac Special Premature 24 Cal Care 20 with Iron HP [R] (A)	24 20	27/29 (20:80) 20.3	Nonfat milk, whey protein concentrate	88/85 69.7	Corn syrup solids, lactose Corn syrup solids, lactose
Similac Special Enfamil Premature 24 Cal [R]/Similac Special Care 24 Cal [R] (A)	24 24	27/29 26.8 (20:80)	Nonfat milk, whey protein concentrate	83.6/81 88/85	Corn syrup solids, lactose
Similac Special Enfamil Premature 30 Cal [R] (A)	30 24	33 (20:80) 24.5/26.8	Nonfat milk, whey protein concentrate	109 83.6/81	Corn syrup solids, lactose
Similac Special Care 30 with Iron Enfamil [R] (A)	30	30.4	Nonfat milk, whey protein concentrate	78.4	Corn syrup solids, lactose
Premature 30 Cal [R] (MJ)	30	33 (20:80)	Nonfat milk, whey protein concentrate	109	Maltodextrin, rice st lactose
Formulas for Premature Infants: Transition or Postdischarge					
Similac Special Care 30 with Iron Enfamil [R] (A)	30 22	30.4 21 (20:80)	Nonfat milk, whey protein concentrate	78.4 77	Corn syrup solids, Powder = corn syrup solids, lactose
NeuroPro			concentrate		

Trade Name [form] (Mfr)	Energy Content ^a (kcal/ oz)	Protein ^a (g/ L) (C:W ratio)	Protein Source(s)	Carbohydrate ^a (g/ L)	Carbohydrate Source(s)
EnfaCare [P,R] (MJ)			concentrate		
Formulas for Premature Infants: Transition or Postdischarge					
Enfamil EnfaCare					Liquid = maltodextrin, lactose
[R]/Enfamil NeuroPro	22	21 (20:80)	Nonfat milk, whey protein concentrate	77	Powder = corn syrup solids, lactose
Enfacare [P,R] Similac NeoSure (MJ) [P,R] (A)	22	20.8	Nonfat milk, whey protein concentrate	75.1	Corn syrup solids, lactose
					Liquid = maltodextrin, lactose
Older Infant/Toddler Milk-Based Formulas					
Similac NeoSure [P,R] (A)	22	20.8	Nonfat milk, whey protein concentrate	75.1	Corn syrup solids, lactose (70%), corn lactose
Deha Good Start Gentle 2 ^{d,e} [P] (G)	20	15.4 (0:100)	partially hydrolyzed concentrate (milk)	79.4	maltodextrin (30%), galacto- oligosaccharides
Older Infant/Toddler Milk-Based Formulas					
Go & Grow by Gerber Good Similac Toddler Start Gentle 2 ^{d,e} Drink [P] (A) [P] (G)	19 20	16.7 15.4 (0:100)	100% whey protein partially hydrolyzed concentrate (milk)	66.7 79.4	Lactose, sucrose, corn syrup solids, maltodextrin (30%), galacto- oligosaccharides
Enfagrow by Similac Toddler Drinks [P] (A) [P,R] (A) (MJ)	19 20	16.7 17.6 (80:20)	Nonfat milk Nonfat milk	66.7 73	Lactose, sucrose, Corn syrup solids, galacto- lactose, galacto- oligosaccharides
Enfagrow					
Premium Toddler Enfagrow Transitions [P,R] Toddler (MJ) Transitions- Gentlease [P]	20 20	17.6 (80:20) 17.6 (40:60)	Nonfat milk hydrolyzed nonfat milk, whey protein	73 71	Corn syrup solids, lactose, galacto- Corn syrup solids, oligosaccharides, galacto- oligosaccharides

Trade Name [form] (Mfr)	Energy Content ^a (kcal/ oz)	Protein ^a (g/ L) (C:W ratio)	Protein Source(s)	Carbohydrate ^a (g/ L)	Carbohydrate Source(s)
(MJ)			concentrate solids (soy)		
Enfagrow Toddler Gerber Good Transitions- Start Grow 3 ^{d,e} Gentlease [P] [P] (G) (MJ)	20 20	17.6 (40:60) 20.5	Partially hydrolyzed nonfat milk, whey protein concentrate solids (soy)	71 82.1	Corn syrup solids, galactooligosaccharides
Soy-Based Products					
Gerber Good Start Grow 3 ^{d,e} Enfagrow [P] (G) Toddler	20 20	20.5 22	Nonfat milk Soy protein isolate, L- methionine, taurine	82.1 80	Corn maltodextrin, sugar Corn syrup solids
Soy-Based Products					
Enfagrow Toddler Stage 3 Gerber Transitions Soy Good Start Soy ^e [P] (MJ) [P] (G)	20 20	22 15.8	Enzymatically Soy protein hydrolyzed isolate, L- soy protein methionine, isolate, L- taurine methionine, taurine, L- carnitine	80 72.7	Corn syrup solids Corn maltodextrin (sucrose (21%)
Go & Grow by Stage 3 Gerber Toddler Start Soy ^e [P] (A)	19 20	16.7 15.8	Enzymatically hydrolyzed Milk protein isolate, L- methionine, taurine, L- carnitine	66.8 72.7	Corn syrup, sugar, galactooligosaccharides (21%)
Children's Formulas					
PediaSure Grow	30	30	Milk protein	139	Corn maltodextrin,

Trade Name [form] (Mfr)	Energy Content ^a (kcal/ oz)	Protein ^a (g/ L) (C:W ratio)	Protein Source(s)	Carbohydrate ^a (g/ L)	Carbohydrate Source(s)
& Gain Therapeutic Nutrition Shake/ PediaSure Sensitive Enteral Formula [R] (A) [R] (A)	19	16.7	concentrate, soy protein Milk protein isolates	66.8	Sugar syrup, sugar, galacto- oligosaccharides
Children's Formulas					
PediaSure 1.5 Cal PediaSure Grow [R] (A), vanilla & Gain	45	59	Milk protein concentrate	160	Corn maltodextrin
Therapeutic Nutrition Shake/ PediaSure Enteral Formula PediaSure [R] (A)	30	30	Milk protein concentrate, soy protein isolates	139	Corn maltodextrin, sugar
PediaSure 1.5 Cal PediaSure Grow and Gain with Fiber ^o /PediaSure Enteral Formula PediaSure 1.5 Cal 1.0 Cal with [R] (A), vanilla Fiber ^o [R] (A)	30 45	30 59	Milk protein concentrate; soy protein isolates (Grow and Gain only)	139/143 (13 g/L of dietary fiber ^o) 160	Corn maltodextrin, sugar, short-chain fructo-oligosacchar Soy fiber, oat fiber
PediaSure 1.5 Cal with Fiber ^o [R] (A) PediaSure Enteral Formula 1.0 Cal with Fiber ^o [R] (A)	45 30	59 30	Milk protein concentrate; soy protein isolates (Grow and Gain only)	166 (13 g/L of dietary fiber with 6.3 g/L of 139/143 (13 g/L of scFOSs ^o) dietary fiber ^o)	Corn maltodextrin, short-chain fructo- Corn maltodextrin, oligosaccharides, o sugar, short-chain fructo-oligosacchar soy fiber, oat fiber
Nutren Junior [R]/Nutren Junior with Fiber ^P [R] (Nes) PediaSure 1.5 Cal with Fiber ^o [R] (A), vanilla	30 45	30 (50:50) 59	Milk protein concentrate, 50% whey protein concentrate (milk) Milk protein concentrate Soy protein isolate, Milk protein concentrate, 50% whey protein protein broth	112/116 (6 g/L of dietary fiber as PreBio) ^P 166 (13 g/L of dietary fiber with 6.3 g/L of scFOSs ^o)	Maltodextrin, sugar fiber product also contains pea fiber, fructo-oligosacchar Corn maltodextrin, short-chain fructo- oligosaccharides, o Organic banana pur fiber, soy fiber organic spinach pur organic milled whol Maltodextrin, sugar fiber product also contains pea fiber fructo-oligosacchar puree, organic rice

Trade Name [form] (Mfr)	Energy Content ^a (kcal/ oz)	Protein ^a (g/ L) (C:W ratio)	Protein Source(s)	Carbohydrate ^a (g/ L)	Carbohydrate Source(s)
			concentrate (milk)		maltodextrin, organic inulin, stevia leaf extract, carrot juice
Boost Kid Essentials [R] (Nes)	30	29.2	Sodium and calcium caseinate (solid), whey protein (solid)	133.3	Organic banana puree, organic spinach puree, maltodextrin, sugar, inulin, stevia leaf extract
PediaSure Harvest [R] (A)	20	38	protein rice protein concentrate	131 (8 g/L as fiber)	organic mango puree, organic broccoli puree, organic pumpkins puree, organic rice maltodextrin, organic Brown rice syrup In carrot juice containing products:
Boost Kid Essentials 1.5 [R]/Boost Kid Essentials 1.5 with Fiber [R] (Nes)	45	42.2	concentrate, chicken broth		gum acacia, pea fiber
Boost Kid Essentials 1.5 with Fiber [R] (Nes)			Milk protein concentrate	164.6/173 (8.3 g/L of fiber)	
Essentials [R] (Nes)	30	29.2	Sodium and calcium caseinates (milk), whey protein Dehydrated concentrate chicken	133.3	Maltodextrin, sugar Brown rice syrup fr and vegetable blend (tomato paste, green bean powder, peach puree, carrot powder, cranberry juice Brown rice syrup In concentrate, pea containing products: powder), pea fiber, gum acacia, pea fiber, fructo-oligosaccharide, inulin
Compleat Boost Kid Pediatric ^a [R] Essentials 1.5 (Nes)	30	38	powder, pea protein	136 (6.8 g/L of Nutrisource Fiber)	
[R]/Boost Kid Essentials 1.5 with Fiber [R] (Nes)	45	42.2	isolate, milk Milk protein protein concentrate concentrate	164.6/173 (8.3 g/L of fiber)	
Carnation Breakfast Essentials [R] (Nes)	30	41.7	Milk protein Dehydrated concentrate, chicken soy protein powder, pea isolate protein	170.8	Brown rice syrup, fr and vegetable blend (tomato paste, green bean powder, peach puree, carrot powder, cranberry juice concentrate, pea powder), pea fiber, fructo-oligosaccharide, inulin
Compleat Pediatric ^a [R] (Nes)	30	38	isolate, milk	136 (6.8 g/L of Nutrisource Fiber)	
Other Therapeutic Formulas—Older Infants, Toddler, and Pediatric Formulations			protein concentrate		
Nectar Splash Pediatric ^a [R] Essentials [R] (Nes)	30 30	30 41.7	Milk protein Free L-amino concentrate, acids soy protein isolate	105 170.8	Maltodextrin, sugar Corn syrup, sugar

Trade Name [form] (Mfr)	Energy Content ^a (kcal/ oz)	Protein ^a (g/ L) (C:W ratio)	Protein Source(s)	Carbohydrate ^a (g/ L)	Carbohydrate Source(s)
Other Therapeutic Formulas—Older Infants, Toddler, and Pediatric Formulations					
EleCare Jr [P] (A), flavored or unflavored	30	31	Free amino acids	106.7	Corn syrup solids
Neocate Splash [R] (Nut), unflavored	30	30	Free L-amino acids	105	Maltodextrin, sugar
Neocate Junior ⁱ [P] (Nut), flavored or unflavored	30	31	Free L-amino acids	107 (unflavored; varies for flavored)	Corn syrup solids, CITREM
EleCare Jr [P] (A), flavored or unflavored	30	31	Free amino acids	106.7	Corn syrup solids
PurAmino Jr [P] (MJ), flavored or unflavored	30	28	Free amino acids	121	Corn syrup solids, modified tapioca st
Neocate Junior ⁱ [P] (Nut), flavored or unflavored	30	31	Free L-amino acids	107 (unflavored; varies for flavored)	Corn syrup solids, Maltodextrin, sugar
Peptamen Junior [R] (Nes), flavored and unflavored	30	30 (0:100)	Enzymatically hydrolyzed whey protein (milk)	136	Maltodextrin, sugar corn starch, monk f juice concentrate, g gum, sucralose
Peptamin Junior HP [R] (Nes), PurAmino Jr [P] vanilla (MJ), flavored or unflavored	36 30	48 (0:100) 28	Enzymatically hydrolyzed whey protein (milk) Free amino acids	152 (4 g/L of PreBio ^P fiber) 121	Maltodextrin, sugar corn starch, monk f juice concentrate, g gum, sucralose, fructo oligosaccharides, in
Peptamen Junior [R] (Nes), 1.5 ^P [R] (Nes), flavored and unflavored	30 45	30 (0:100) 46 (0:100)	Enzymatically hydrolyzed whey protein (milk) Enzymatically hydrolyzed whey protein (milk)	184 (6 g/L of soluble dietary fiber) 136	Maltodextrin, sugar Maltodextrin, monk f juice concentrate, g gum, sucralose, fructo oligosaccharides, in
Peptamin Junior HP [R] (Nes), Peptamen Junior	36 30	48 (0:100) 30 (0:100)	Enzymatically hydrolyzed Enzymatically	152 (4 g/L of PreBio ^P fiber) 144 (4 g/L of	Maltodextrin, sugar corn starch, monk f Maltodextrin, sugar

Trade Name [form] (Mfr)	Energy Content ^a (kcal/ oz)	Protein ^a (g/ L) (C:W ratio)	Protein Source(s)	Carbohydrate ^a (g/ L)	Carbohydrate Source(s)
vanilla Fiber [R] (Nes)			whey protein hydrolyzed (milk) whey protein (milk)	soluble fiber, 4 g/L of insoluble fiber)	juice starch, partially hydrolyzed gligosaccharides, gum monk fruit juice concentrate, sucralose
Peptamen Junior 1.5 ^P [R] (Nes), flavored or Pediasure unflavored Peptide 1.0 Cal ^o [R] (A), vanilla	45 30	46 (0:100) 30	Enzymatically hydrolyzed whey protein hydrolysate, (milk) hydrolyzed sodium caseinate	184 (6 g/L of soluble dietary fiber, 3 g/L of dietary fiber, 3 g/L of scFOSs ^o)	Maltodextrin, corn starch, partially hydrolyzed guar gum, short-chain fructo- oligosaccharides
Peptamen Junior Fiber [R] (Nes) Pediasure Peptide 1.5 Cal ^o [R] (A), flavored (vanilla)	30 45	30 (0:100) 45.1	Enzymatically hydrolyzed whey protein (milk) hydrolysate, hydrolyzed sodium caseinate Whey protein hydrolysate, hydrolyzed 100% free L- amino acids	144 (4 g/L of soluble fiber, 4 g/L of insoluble fiber, 4.6 g/L of dietary fiber, 4.6 g/L of scFOSs ^o)	Maltodextrin, sugar corn starch, pea fiber, partially hydrolyzed guar gum, guar gum, corn maltodextrin, sugar, short-chain fructo-oligosaccharides
Pediasure Peptide 1.0 Cal ^o Vivonex [R] (A), vanilla Pediatric ^r [P] (Nes)	30 24	30 24	100% free L- amino acids	134 (3 g/L of dietary fiber, 3 g/L of scFOSs ^o) 128	Corn maltodextrin, short-chain fructo- oligosaccharides, Maltodextrin, modified corn starch
Portagen [P] (Pediasure) Peptide 1.5 Cal ^o [R] (A), flavored (vanilla)	30 45	35.4 45.1	Sodium Whey protein caseinate hydrolysate, hydrolyzed Sodium (milk), caseinate (milk), whey (milk), L-tryptophan, sodium caseinate (100% free L- amino acids, taurine	114.6 201 (4.6 g/L of dietary fiber, 4.6 g/L of scFOSs ^o)	Corn syrup solids, sugar Corn maltodextrin, sugar, short-chain fructo-oligosaccharides
KetoCal 3:1 ^s [P] (Nutr) Vivonex Pediatric ^r [P] (Nes)	30 24	22 24	100% free L- amino acids, taurine	10 128	Lactose, corn syrup solids, Maltodextrin, modified corn starch
Portagen [P] (Nutr) Cal 4:1 ^s [P] (Nutr)	30 30	35.4 20	Casein (milk), Sodium whey (milk), caseinate L-tryptophan, sodium caseinate	114.6 12 (7.5 g/L of dietary fiber)	Microcrystalline cellulose, sucralose, inulin, corn syrup solids, fructo-oligosaccharides, high amylase corn

Trade Name [form] (Mfr)	Energy Content ^a (kcal/ oz)	Protein ^a (g/ L) (C:W ratio)	Protein Source(s)	Carbohydrate ^a (g/ L)	Carbohydrate Source(s)
KetoCal 3:1 ^s [P] (Nutr)	30	22	(milk), whey (milk), phenylalanine, L-tyrosine, L- tryptophan, lysine, L- cysteine, (milk), L- histidine, taurine	10	starch, soy fiber, Lactose, corn syrup solids, sucralose
KetoCal 4:1 LQ ^s [R] (Nutr)	45	30.9	Caseinate (milk), (milk), (milk), phenylalanine, tryptophan, sodium citrate (milk), L- cysteine, (milk), L- phenylalanine, taurine, L- tryptophan	17.3 (11.2 g/L of dietary fiber)	Soy fiber, corn starch, Microcrystalline inulin, microcrystalline cellulose, chicory root cellulose, fructo- inulin, corn syrup solids, oligosaccharide, fructo-oligosaccharide
KetoCal 4:1 ^s [P] (Nutr)	30	20	(milk), L- phenylalanine, taurine, L- tryptophan, carnitine, sodium L- histidine	12 (7.5 g/L of dietary fiber)	high amylase corn starch, soy fiber, sucralose
KetoCal 2.5:1 LQ ^{i,s} [R] (Nutr)	45	45	(milk), whey protein concentrate (milk), whey protein, L- cysteine, (milk), L- cystine, L- carnitine, taurine, L- tryptophan	22 (11 g/L of dietary fiber)	Sugar, soy fiber, corn starch, inulin, CITRE microcrystalline cellulose, fructo- oligosaccharides, Soy fiber, corn starch, maltodextrin, sucra
KetoCal 4:1 LQ ^s [R] (Nutr)	45	30.9	(milk), L- cysteine, L- carnitine, taurine, L- tryptophan	17.3 (11.2 g/L of dietary fiber)	cellulose, fructo- oligosaccharide,
Note: Federal regulations require nutrient values to be reported as intakes per 100 kcal. These intakes can be found on the manufacturer's website. Values per liter of formula are provided for ease of calculation. Changes are made periodically in formula composition; for the most up-to-date information, refer to the manufacturer's website.					
^a When powder is prepared to achieve the stated caloric density. KetoCal 2.5:1 LQ ^{i,s} [R] (Nutr) is a new formulation [R, P] with C:W ratio of 20:80. It provides sufficient vitamin D (400 international units) in minimum volume of 27 fl oz.	45	45	(milk), whey protein concentrate (milk), L- cystine, L- carnitine, taurine	22 (11 g/L of dietary fiber)	Sugar, soy fiber, corn starch, inulin, CITRE microcrystalline cellulose, fructo- oligosaccharides, maltodextrin, sucra
^c Has one-fifth the lactose content of standard milk-based formula.					

^d Contains *Bifidus* BL (*Bifidobacterium lactis*), which is similar to probiotics found in

Note: Federal regulations require nutrient values to be reported as intakes per 100 kcal. These intakes can be found on the manufacturer's website. Values per liter of formula are provided for ease of calculation. Changes are made periodically in formula composition; for the most up-to-date information, refer to the manufacturer's website.

^f Product available as non-GMO-based option.

^a When powder is prepared to achieve the stated caloric density.

^g Product content depends on formulation (i.e., ready-to-feed, powder, or concentrate).

^b Available as newborn formulation [R, P] with C:W ratio of 20:80. Provides sufficient

^h Powder form available as Nutramigen with Enflora LGG. vitamin D (400 international units) in minimum volume of 27 fl oz.

ⁱ Product contains CITREM (citric acid esters of mono- and diglycerides).

^c Has one-fifth the lactose content of standard milk-based formula.

^j When carbohydrate is added as directed to make a 20 kcal/oz concentration. For RCF:

^d Contains *Bifidus* BL (*Bifidobacterium lactis*), which is similar to probiotics found in 54 g of carbohydrate + 12 fl oz water + 13 fl oz of RCF to yield 26 fl oz. For 3232A: 81 g of human milk. 3232A + 59 g carbohydrate per quart prepared.

^e Standard product available as non-genetically modified organism (GMO)-based.

^k Marketed as the only infant formula available for the ketogenic diet.

^f Product available as non-GMO-based option.

^l Potential option for infants with disaccharidase deficiencies.

^g Product content depends on formulation (i.e., ready-to-feed, powder, or concentrate).

^m Percentage of daily value for children 1–4 years of age.

^h Powder form available as Nutramigen with Enflora LGG.

ⁿ Percentage of daily value for diet of 2000 kcal.

ⁱ Product contains CITREM (citric acid esters of mono- and diglycerides).

^o Prebiotic Nutraflora scFOSs are short-chain fructo-oligosaccharides that provide fuel

for beneficial bacteria in the digestive tract to help support a healthy immune system. When carbohydrate is added as directed to make a 20 kcal/oz concentration. For RCF:

54 g of carbohydrate + 12 fl oz water + 13 fl oz of RCF to yield 26 fl oz. For 3232A: 81 g of

^p PreBio is a unique blend of fructo-oligosaccharides and inulin. These compounds 3232A + 59 g carbohydrate per quart prepared.

may increase colonic mucosal integrity and permeability, promote potentially

beneficial bacteria, and improve colonic absorption of water and electrolytes.

^k Marketed as the only infant formula available for the ketogenic diet.

^q Available in various options, including Organic Blends Plant-Based Option and

potential option for infants with disaccharidase deficiencies.

Organic Blends, Chicken-Garden Blend Option. Reduced calorie option also available

as 20 kcal/oz and daily used for children 1–4 years of age gain associated with

developmental delay.

ⁿ Percentage of daily value for diet of 2000 kcal.

^r Prepared utilizing 1 packet to produce 250 mL of formula (1.7 oz + 220 mL of water =

^q Prebiotic Nutraflora scFOSs are short-chain fructo-oligosaccharides that provide fuel 250 mL of formula).

for beneficial bacteria in the digestive tract to help support a healthy immune system.

^s Ratio denotes fat/carbohydrate + protein composition.

^p PreBio is a unique blend of fructo-oligosaccharides and inulin. These compounds

Key Areas of Nutrition: C:W ratio, carbohydrate, protein, fat, electrolytes, probiotics, prebiotics, and

beneficial bacteria. These compounds improve colonic absorption of water and electrolytes.

= manufacturer; MJ = Mead Johnson Nutrition; Nes = Nestlé Nutrition; Nut = Nutricia

North America, P = powder; R = ready-to-feed; scFOSs = short-chain fructo-oligosaccharides; Chicken-Garden Blend Option. Reduced calorie option also available as 18 kcal/oz and marketed for disproportionate weight gain associated with developmental delay. Source: Abbott Nutrition (www.abbottnutrition.com); Gerber (medical.gerber.com); Mead Johnson Nutrition (www.meadjohnson.com); Nestlé Healthcare Nutrition (<http://www.nestlehealthscience.us>); and Nutricia North America (www.nutricia-na.com). Accessed May 16, 2019.

^s Ratio denotes fat/carbohydrate + protein composition.

Key: A = Abbott Nutrition; ARA = arachidonic acid; C = concentrate; C:W = casein/whey ratio; DHA = docosahexaenoic acid; G = Gerber; MCTs = medium chain triglycerides; mfr = manufacturer; MJ = Mead Johnson Nutrition; Nes = Nestlé Nutrition; Nut = Nutricia North America; P = powder; R = ready-to-feed; scFOSs = short-chain fructo-oligosaccharides.

Source: Abbott Nutrition (www.abbottnutrition.com); Gerber (medical.gerber.com); Mead Johnson Nutrition (www.meadjohnson.com); Nestlé Healthcare Nutrition (<http://www.nestlehealthscience.us>); and Nutricia North America (www.nutricia-na.com). Accessed May 16, 2019.

Formula Properties

The International Formula Council is a voluntary, nonprofit trade association composed of the five companies that manufacture and market infant formulas and adult nutritionals: Abbott Nutrition, Mead Johnson Nutrition, Nestlé Infant Nutrition, Perrigo Nutritionals, and Pfizer Nutrition. This association has established guidelines requiring liquid formulations to be free of all viable pathogens, including spores, and other organisms that may cause product degradation. In addition, infant formula constituents must meet certain concentrations to ensure optimum nutrition. In accordance with the FDA's Infant Formula Act of 1980, standards have been established to ensure safety and efficacy of infant formulas.

Microbiologic Safety

Manufacturers sterilize liquid formulas using heat treatment, and the product is free of microbes so long as the container remains intact. Powdered formulas are not required or guaranteed to be sterile; however, coliforms and other

pathogens are absent, and levels of contamination with other microorganisms are below acceptable government standards. If clinically significant microbiologic contamination occurs, an infant ingesting the formula could develop diarrhea with subsequent fluid and electrolyte losses. In 2002, FDA issued an alert after the death of an infant in a neonatal intensive care unit after consumption of powdered formula contaminated with *Cronobacter* (formerly *Enterobacter*) *sakazakii* at the manufacturing site. Information regarding potential contamination can be found on the CDC website (www.cdc.gov/features/cronobacter).

Risk for infection after exposure to contaminated formula is likely to depend on a number of factors, including the infant's immune status. Accordingly, for premature and immunocompromised infants, use of ready-to-feed or liquid concentrates is recommended unless no suitable alternative to a powdered formula is available.

Physical Characteristics

Infant formulas are emulsions of edible oils in aqueous solutions, but fat separation rarely occurs. If it does, shaking the container usually will redisperse the fat. Redispersion may not be achievable if stabilizers are lacking or if the formula was stored beyond its shelf life. Liquid infant formulas may contain thickening agents, stabilizers, and emulsifiers to provide uniform consistency and prolong stability. Protein agglomeration may occur, however, if storage time is excessive. Evidence of such agglomeration ranges from development of a slightly grainy consistency through increased viscosity and gel formation to eventual protein precipitation. Agglomeration and separation do not affect a formula's safety or nutritional value; however, the formula's appearance may deter caregivers from using it.

Caloric Density

The standard caloric density for infant formulas is 20 kcal/oz, or approximately 67 kcal/100 mL, which mimics the historical average caloric density of human milk. One exception is selected standard infant formulas manufactured by Abbott Nutrition that, if prepared according to standard preparation instructions, provide 19 kcal/oz, or approximately 65 kcal/100 mL ([Table 26–6](#)). According to the manufacturer, this change reflected newer information indicating that the caloric density of term breast milk is closer to 19 kcal/oz.

Subsequently, however, Abbott decided to convert all of its infant formulas back to a standard 20 kcal/oz, beginning in 2019 with the Similac Advance milk-based formula products and continuing with the other infant formulas throughout 2020 (www.nutritionnews.abbott).

A healthy term infant should have no difficulty consuming enough formula to meet both energy (calorie) and fluid needs with the standard caloric density of 20 kcal/oz. Premature, malnourished, volume-restricted (e.g., for cardiac or liver disease or from poor oral feeding), or severely ill infants may require more calories (130–150 kcal/kg/day or higher) or formulas with higher caloric densities (e.g., 22, 24, or 27 kcal/oz) to meet their energy needs. Infant formulas with caloric densities significantly lower or higher than 20 kcal/oz are regarded as *therapeutic formulas* to be used in managing special clinical conditions (Tables 26–6 and 26–7). Concentrated formulas should be used only under close medical supervision, especially with monitoring for dehydration caused by the reduction in free water consumed.

Osmolality and Osmolarity

Osmolality is the preferred term for reporting the osmotic activity of infant formulas. Osmolality represents the number of osmoles of solute per kilogram of solvent (Osm/kg). Any dietary component soluble in water contributes to osmolality. Osmolality is directly related to the concentration of molecular or ionic particles in the solution (i.e., amino acids, small peptides, electrolytes, and simple sugars) and inversely proportional to the concentration of water in the formula. The osmolality of human milk is approximately 295 mOsm/kg; osmolality of standard-caloric-density formulas is 200–300 mOsm/kg.

The *osmolarity* of an infant formula may be expressed as the concentration of solute per unit of total volume of solution, or as the number of osmoles of solute per liter of solution (Osm/L). The osmolarity of human milk is approximately 273 mOsm/L. Formulas for infants should have osmolarities no higher than 400 mOsm/L. Unless the formula is very concentrated, there is no meaningful difference between osmolality and osmolarity of infant formulas.

The osmolality of a formula increases with increasing caloric density. The relationship between osmolality and caloric density is reasonably linear within the range of caloric concentrations usually fed to infants. Thus, if the osmolality of a 20 kcal/oz formula is known, the same formula with any other caloric

density can be calculated, assuming a direct proportion between osmolality and caloric density. For example, if a 20 kcal/oz formula has an osmolality of 283 mOsm/kg, then the same formula concentrated to 24 kcal/oz would have an osmolality of approximately 340 mOsm/kg.

No clinically meaningful differences in osmolality have been noted for the various 20 kcal/oz, ready-to-use formulas in common use. In addition, when concentrated products are diluted to yield a formula providing 20 kcal/oz, no meaningful difference in osmolality is seen relative to the similar ready-to-use product. However, directions for diluting concentrated and powdered formulas must be followed exactly. Soy protein-based formulas have somewhat lower osmolalities than milk-based formulas because of the difference in carbohydrate source.

Potential Renal Solute Load

The PRSL is the solute load derived from the diet that must be excreted by the kidney if the amino acids from protein digestion are not used for growth or eliminated by nonrenal routes. The PRSL for an infant formula can be calculated using the following equation: $\text{PRSL (mOsm)} = \text{N}/28 + \text{sodium} + \text{chloride} + \text{potassium} + \text{phosphorus(available)}$, where N is total nitrogen content in milligrams, and concentrations of sodium, chloride, potassium, and phosphorus(available) (P_a) are expressed in millimoles (or milliosmoles), typically measured per liter of formula. The P_a is assumed to be the total phosphorus content except in soy-based formulas, in which it represents only two thirds of the total phosphorus. [Table 26–5](#) lists PRSLs for various milks and infant formulas compared with the FDA-recommended upper PRSL limit.⁵³ Excretion of 1 mOsm of ingested solute requires 1 mL of water intake. Standard 20 kcal/oz infant formulas supply approximately 1.5 mL of water per kilocalorie ingested, an adequate amount of water to provide usual needs. Accordingly, when the infant is healthy, the PRSL generally is not a consideration in hydration; however, during illnesses associated with water loss, such as vomiting, diarrhea, and fever, or in infants with compromised renal function or diabetes insipidus, the formula's PRSL becomes a factor in maintaining fluid balance. Feeding a formula with a high PRSL (i.e., high protein content or concentrated to more than 24 kcal/oz) may produce a hypertonic urine, leading to increased renal water losses and dehydration.

Types, Uses, and Selection of Commercial Infant

Formulas

Standard formulas for term infants are milk-based, or milk-based with added whey protein (whey-predominant). Other formulas are available for infants and children with specific dietary needs and should be used only under medical supervision.

Milk-Based Formulas

Milk-based formulas ([Table 26–6](#)) are prepared from nonfat cow milk, vegetable oils, and added carbohydrate (lactose). The added carbohydrate is necessary, because the ratio of carbohydrate to protein in nonfat cow milk solids is less than desirable for infant formulas. The most widely used vegetable oils are corn, coconut, safflower, sunflower, palm olein, and soy. Replacement of the butterfat with vegetable oils allows for better fat absorption. Although Similac Sensitive and Similac Total Comfort are milk-based formulas, they contain sucrose with corn maltodextrin, rather than lactose, as the carbohydrate source and may be used for infants with lactose intolerance. Enfamil Gentlease and Gerber Good Start Soothe contain decreased lactose amounts (20% and 30%, respectively) when compared with the relevant product line's standard milk-based formulas, and both are marketed for infant colic.

Therapeutic Formulas

Therapeutic infant formulas are used for infants with conditions requiring dietary adjustment and should be used with medical supervision, rather than being self-selected by parents. [Table 26–7](#) lists indications for various therapeutic formulas, including soy protein-based, casein-based, casein hydrolysate-based, and whey hydrolysate-based formulas and low-electrolyte and low-mineral formulas. Formulas intended for use in premature infants and those formulated specifically for children 1–10 years of age also are considered therapeutic formulas.

Table 26–7 Indications for Therapeutic Infant Formulas^a

Problem/ Indication	Suggested Therapeutic Formula(s)	Comments
Allergy or	EleCare (for Infants), Neocate	Protein hydrolysate or free amino acid

Problem/ Indication	Suggested Therapeutic Formula(s)	Comments
sensitivity to cow milk or soy protein	Infant DHA & ARA, Nutramigen, PurAmino, Pregestimil, Similac Alimentum, Gerber Extensive HA	formula is best.
		Up to 50% cross-sensitivity between cow milk and soy protein allergies is possible.
Biliary atresia, cholestatic liver disease	EleCare (for Infants), Enfaport, Pregestimil, Similac Alimentum	Impaired digestion and absorption of long-chain fats; higher percentage of MCTs may improve absorption.
Carbohydrate intolerance (severe)	3232A, RCF	These are carbohydrate-free products.
		A patient-tolerated carbohydrate source is added gradually (e.g., dextrose, glucose, sucrose, fructose).
Cardiac disease	No therapeutic formula generally necessary	Low electrolyte content (Similac PM 60/40) is indicated if infant has renal insufficiency.
		Electrolyte supplementation may be needed in patients receiving diuretics.
		Calorically dense, standard formulas often used in cases of failure to thrive and for volume restriction.
Celiac disease	EleCare (for Infants), Neocate Infant DHA & ARA, Nutramigen, PurAmino, Pregestimil, Similac for Diarrhea	Advance to standard formulas as intestinal epithelium returns to normal; diet must be gluten-free.
Chylothorax or chylous ascites	Enfaport	High MCT intake decreases flow through the lymphatic system.
Constipation	No therapeutic formula necessary	Continue routine formula; increase water; refer cases of severe constipation.
Cystic fibrosis	EleCare (for Infants), Pregestimil, Similac Alimentum, Gerber	Impaired digestion and absorption of long-chain fats; cow milk-based formula

Problem/ Indication	Suggested Therapeutic Formula(s)	Comments
	Extensive HA	or human milk may be used with appropriate pancreatic enzyme supplementation.
		Enzyme supplementation may be required even with predigested therapeutic formulas; soy protein-based formulas are contraindicated.
Diarrhea, chronic nonspecific	Enfamil ProSobee, Nutramigen, Similac Soy Isomil, Gerber Good Start Soy	Trial of lactose-free cow milk or soy protein-based formula may be needed; avoid fruit juices.
Diarrhea, intractable	3232A, EleCare (for Infants), PurAmino, Pregestimil, RCF, Similac Alimentum	Hydrolyzed protein is needed because of impaired digestion of intact protein, long-chain fats, and disaccharides.
		Similac Alimentum contains sucrose and may not be appropriate for all cases.
Diarrhea, antibiotic-associated	Similac for Diarrhea	Contains added dietary fiber from soy and was specifically formulated for infants with diarrhea secondary to antibiotics; use short term until diarrhea resolves.
Failure to thrive	No therapeutic formula generally necessary	Most cases related to inadequate intake.
		Start with standard formula; may need more calorically dense formula for catch-up growth; change to predigested formula only if malabsorption is present.
Galactosemia	Enfamil ProSobee, Similac Soy Isomil, Gerber Good Start Soy, Nutramigen, Pregestimil	Formulas without lactose or sucrose; cow and human milk are contraindicated.
Gastroesophageal reflux	Enfamil A.R., Similac For Spit-Up	Recommend use of thickened commercial formulas as first line therapy. If using standard formula thickened with rice cereal, start with 1–2 teaspoons/oz of formula and increase to a maximum of 1 tablespoon/oz as

Problem/ Indication	Suggested Therapeutic Formula(s)	Comments
		tolerated.
		Thickening formula with rice cereal increases the caloric density, may cause constipation, results in delivery of less volume, and usually requires enlarging the nipple, which increases risk for aspiration.
		Some infants may have an allergic-type reaction to rice cereal; oatmeal may be used in such cases.
		Attempt small, frequent feedings; avoid using products like Thick-It and SimplyThick to thicken formula (these products are intended for patients with dysphagia or swallowing difficulties); use more calorically dense formula if decreased volume or catch-up growth is needed.
Hepatitis without liver failure	No therapeutic formula necessary	Impaired digestion or absorption of long-chain fats is uncommon.
Hepatitis with liver failure	EleCare (for Infants), Enfaport, Pregestimil, Similac Alimentum	Digestion or absorption of long-chain fats may be impaired.
Increased ostomy output	Similac for Diarrhea, Elecare (for Infants), Neocate Infant DHA & ARA	Improve consistency in term infants without malabsorption (e.g., Hirschsprung disease, imperforate anus, necrotizing enterocolitis, intestinal atresias).
		More elemental formulas may be required for malabsorption.
Lactose intolerance (primary or secondary)	Enfamil ProSobee, Similac Soy Isomil, Gerber Good Start Soy	Remove lactose from diet; use lactose-free formula.
Necrotizing enterocolitis (during recovery	EleCare (for Infants), Neocate Infant DHA & ARA, Pregestimil, Similac Alimentum	Impaired digestion or absorption requires a hydrolysate or free amino acid formula.

Problem/ Indication	Suggested Therapeutic Formula(s)	Comments
or postresection)		
Prematurity	Fortified human milk (preferred); Enfamil Premature 20 Cal, Similac Special Care 20, or transition infant formula (Enfamil EnfaCare or Similac NeoSure); may use more concentrated premature formulas during hospitalization (24–30 kcal/oz)	Human milk fortifier needed; transition formula (see Suggested Therapeutic Formula(s) column) can be added to human milk to increase caloric density after hospital discharge to home (1 teaspoon/90 mL of milk makes 24 kcal/oz).
Refractory seizure disorder	KetoCal, RCF	Dietary management of intractable epilepsy (fat/carbohydrate + protein ratio).
Renal insufficiency	Similac PM 60/40	Formula is low phosphate.

^a Products are listed alphabetically. List is not all-inclusive; other products may be acceptable.

Key: MCT = Medium-chain triglyceride.

Source: Abbott Nutrition (www.abbottnutrition.com); Mead Johnson Nutrition (www.meadjohnson.com); Gerber (www.medical.gerber.com); Nestlé Healthcare Nutrition (www.nestlehealthscience.us); and Nutricia North America (www.nutricia-na.com). Accessed October 26, 2019.

Prethickened Milk-Based Formulas. Enfamil A.R. and Similac For Spit-Up were developed specifically for infants with gastroesophageal reflux. These iron-fortified formulas contain rice starch. Before ingestion, the viscosity of Enfamil A.R. or Similac For Spit-Up is much lower than that of a standard infant formula thickened with rice cereal. Therefore, these formulas flow better through a nipple than standard infant formula thickened with rice cereal. Once they are ingested, however, the viscosity increases dramatically in the stomach's acidic pH, reaching a viscosity equal to that for the combination of standard infant formula plus rice cereal. This effect may be minimized in infants receiving a

histamine type 2 receptor antagonist (e.g., famotidine) or proton pump inhibitor (e.g., omeprazole, lansoprazole, pantoprazole, esomeprazole) for treatment of their gastroesophageal reflux, if the gastric pH is greater than 5.4. Also, Similac For Spit-Up is a lactose-free formula. Neither Enfamil A.R. nor Similac For Spit-Up is recommended for use in premature infants, because neither product will adequately meet their nutritional needs, especially for protein, calcium, and phosphorus. In May 2011, FDA cautioned parents against using thickening agents such as SimplyThick and Thick-It in premature infants because of reports of associated necrotizing enterocolitis. This cautionary statement was expanded to apply in infants of all ages in September 2012 (www.fda.gov).

Soy Protein–Based Formulas. Despite relatively few true indications for soy protein–based formulas, approximately 20% of formulas sold in the United States are soy protein–based, suggesting that these formulas are being selected by parents rather than being prescribed by health care providers.^{35,40} Soy protein–based formulas (Table 26–6) contain a soy isolate fortified with L-methionine; none contain lactose. Soy formulas are a safe and nutritionally sound alternative for achieving normal growth and development in infants who are not fed human milk, who do not tolerate cow milk–based formula, or have galactosemia, or whose parents choose such products for other reasons (e.g., to follow a vegetarian diet). However, because soy formulas have insufficient amounts of calcium, phosphorus, and vitamin D for meeting the increased needs of some children, they are not recommended for infants weighing less than 1800 g. Additionally, even after the infant attains a weight of 1800 g, these formulas may not be adequate to provide optimal growth and to prevent osteopenia of prematurity in the long term.⁵⁶

Food allergy develops in infants, because the immature digestive and metabolic processes may not be completely effective in converting dietary proteins into nonallergenic amino acids. Cow milk protein allergy occurs in 2%–3% of infants and is defined as symptomatology involving the respiratory tract (wheezing), skin (rash), or GI tract (diarrhea and bloody stools) that resolves when cow milk is removed from the diet. The disappearance of symptoms may take up to 2 weeks. To confirm a cow milk allergy, two separate challenges of reintroduction of cow milk are conducted during a symptom-free period; reappearance of the symptoms on both tests is diagnostic. Symptoms of cow milk protein intolerance generally regress within 3–4 years in most children.

Soy protein–based formulas are appropriate for infants with lactose intolerance resulting from lactase deficiency and with documented immunoglobulin E (IgE)–mediated allergy to cow milk protein. However, infants with cow milk protein–induced enteropathy or enterocolitis also are frequently sensitive to soy protein (with cross-sensitivity rates of up to 50%); therefore, AAP-CON recommends protein hydrolysate formulas for these infants.⁵⁶ Most infants suspected of having adverse reactions to milk-based formulas have not experienced life-threatening manifestations. These infants appear to tolerate soy protein–based formulas, which are less expensive and better-tasting than the protein hydrolysate formulas. Routine use of soy protein–based formulas has no proven value in prevention of atopic disease.⁵⁷ Some infants with moderate to severe gastroenteritis will exhibit intolerance to lactose and sucrose because of a temporary lactase and sucrase deficiency. After rehydration, however, most infants with diarrhea or recovering from a diarrhea illness can be managed by continuing their usual nutrition regimen, whether milk-based or soy protein–based.

In addition, soy protein–based formulas are not recommended for infants with cystic fibrosis, because these children do not use soy protein adequately, will lose substantial nitrogen in their stools, and are prone to the development of hypoproteinemia or even anasarca (generalized infiltration of fluid into subcutaneous connective tissue). Formula-fed infants with cystic fibrosis do well nutritionally when given an easily digested formula that contains semi-elemental protein and medium-chain triglycerides (MCTs) (e.g., a casein hydrolysate–based formula). However, studies have shown that infants with cystic fibrosis grow equally well on a regular cow milk–based formula and on human milk so long as adequate pancreatic enzyme supplementation is given.⁵⁸

RCF (historically, Ross Carbohydrate Free) is a soy protein–based formula that contains no carbohydrates and is currently marketed as the only infant formula available for patients requiring the ketogenic diet. Use of this formula is limited to infants unable to tolerate the type or amount of carbohydrates in human milk or infant formulas. A carbohydrate source (sucrose, dextrose, fructose, or glucose polymers) is added gradually in increasing amounts to improve carbohydrate tolerance over time.

Casein Hydrolysate–Based Formulas. Protein in casein hydrolysate–based formulas is supplied by enzymatically hydrolyzed, charcoal-treated casein,

rather than by whole protein. Available products include Pregestimil, Nutramigen, and Similac Alimentum ([Table 26–6](#)). These formulas are classified as semi-elemental and contain nonantigenic polypeptides with molecular masses less than 1200 daltons; therefore, they can be fed to infants who are sensitive to intact milk protein. Casein hydrolysate–based formulas are supplemented with L-cysteine, L-tyrosine, and L-tryptophan, because the concentrations of these amino acids are reduced during the charcoal treatment.

Carbohydrate sources in casein hydrolysate–based formulas vary and include corn syrup solids, modified corn and tapioca starch, corn maltodextrin, and sucrose ([Table 26–6](#)). Glucose polymers found in corn syrup solids, modified corn starch, or corn maltodextrin are particularly useful in infants who have malabsorption disorders and are frequently intolerant of high concentrations of lactose, sucrose, and glucose. In addition, glucose polymers contribute little to the total osmolar load. Low osmolality is an advantage in intestinal disorders in which the osmolar load of disaccharide- or glucose-containing elemental diets may not be tolerated. The formula 3232A is an extensively hydrolyzed casein–based formula with added amino acids that is intended, like RCF, to be used with small amounts of added carbohydrate to gradually improve tolerance. This product contains modified tapioca starch and fat, 82% of which is MCTs.

Hydrolysate formulas usually contain modified fat sources. MCTs typically are included, because they do not require emulsification with bile and are more easily digested and absorbed than long-chain fats. Shorter-chain fatty acids and MCTs are directly absorbed into the portal system, not into the lacteals of the lymphatic system. In addition, MCTs enhance the absorption of long-chain triglycerides and do not require carnitine for transport into the mitochondria, where oxidation and energy production occur. MCTs cannot be the sole source of dietary fat, however, because they do not provide essential fatty acids—an important consideration in prevention of essential fatty acid deficiency. Pregestimil and Similac Alimentum contain DHA and ARA as long-chain fatty acids. Diarrhea can result from MCT malabsorption caused by overfeeding or intestinal mucosal disease.

Use of casein hydrolysate–based formulas for allergy prophylaxis is controversial. The AAP policy statement on hypoallergenic formulas notes that infants at high risk for development of allergy identified by a strong family

history (in both parents or in one parent and a sibling) may benefit from a hypoallergenic formula, but studies are not conclusive.⁵⁶ Currently, no evidence has emerged to support the use of hydrolysate formulas for treating colic, irritability, or gastroesophageal reflux. Although these problems are common in infants, they are rarely a result of an IgE-mediated allergic reaction to cow milk protein.

Extensively hydrolyzed casein formulas are less palatable than standard formulas. If the formula is rejected by the infant when first offered, it should be tried again after a few hours. These products are designed to provide a sole source of nutrition for infants up to 4–6 months of age and a primary source of nutrition for children up to 12 months of age, when indicated. Extended use of hydrolysate formulas as a sole source of nutrition in children older than 6 months requires close medical supervision and monitoring.

Whey Hydrolysate–Based Formulas. Enzymatically hydrolyzed whey protein is another protein source used in infant formulas. Infants who have GI intolerance to cow milk but are not allergic to it often tolerate whey hydrolysate–based formula. The product with this formulation, Gerber Good Start Gentle, is promoted as having a pleasant taste, smell, and appearance. It may be better accepted than casein hydrolysate–based formulas, which parents (and infants) find to differ noticeably from cow milk– and soy protein–based formulas in both appearance and taste. No specific indications are recognized for these products, so they may be chosen according to parent, patient, or nutritional program preference.

Amino Acid–Based Formulas. Occasionally, infants are intolerant of even hydrolyzed casein and require a free amino acid–based formula. Neocate Infant DHA & ARA, EleCare (for infants), and PurAmino contain 100% free amino acids and are considered hypoallergenic. They are used for infants with cow milk protein allergy, multiple food protein allergies, or intolerance to casein hydrolysate formulas.

High MCT Formulas. Enfaport and Portagen are unique formulas because of their high MCT content (i.e., 83% and 87% of the fat content, respectively). They also contain higher concentrations of both lipid- and water-soluble vitamins than those found in casein hydrolysate–based formulas. The higher concentrations of MCTs and vitamins in these formulas help compensate for the impaired digestion and absorption of long-chain fatty acids in patients with pancreatic insufficiency (e.g., cystic fibrosis) or bile acid deficiency (e.g.,

biliary atresia, cholestatic jaundice), or with inability to utilize long-chain fatty acids as with long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency, and those who have undergone intestinal resection. Another use is to decrease lymphatic flow in patients with lymphatic anomalies such as chylothorax and chylous ascites. Since it contains the essential fatty acids of alpha-linolenic and alpha-linoleic acid, Enfaport can be used as the sole dietary source for infants, whereas Portagen can be used as the sole dietary source for children and adults or can be given as a beverage to be consumed with each meal as a supplement. Children with fat malabsorption who receive Portagen are at risk for development of essential fatty acid deficiency. Linoleic acid (e.g., corn or safflower oil, Microlipid) can be given in the diet, either by mixing with the formula if a sterile mixing environment is available or delivered by syringe through a feeding tube for home use, to prevent essential fatty acid deficiency.

Low PRSL Formulas. Similac PM 60/40 is an infant formula with lower mineral (potassium and phosphorus) and protein (1.5 g/100 mL) content and, consequently, lower PRSL than in standard infant formulas. It is most appropriately used for infants with renal insufficiency. Similac PM 60/40 also contains less calcium and iron than in standard infant formulas; supplementation of these minerals may be necessary.

Premature Infant Formulas. The current AAP recommendation is for all premature infants to receive maternal human milk or donor human milk.³⁰ Nutrient intake can be inadequate in human milk-fed premature infants, however, because unfortified human milk does not meet the needs of this population. Because of their increased nutrient needs and somewhat decreased ability to consume an adequate volume, premature infants (especially those born before 34 weeks' gestational age) often need feedings providing a higher caloric density, as well as increased protein, calcium, phosphorus, and other nutrients. The nutritional goal for a preterm infant is to achieve a postnatal growth rate approximating the intrauterine growth rate of a normal fetus of the same corrected gestational age.

No commercially available formula is completely satisfactory for premature infants. Formulas for premature infants ([Table 26–6](#)) share features such as whey-predominant proteins, carbohydrate mixtures of lactose and corn syrup solids, and fat mixtures containing both MCTs and long-chain triglycerides. They differ in electrolyte, vitamin, mineral, protein, and caloric content. When given in sufficient volume, these formulas promote adequate growth in

preterm infants. An isotonic osmolality (approximately 300 mOsm/kg of water) is maintained at a caloric density of 24 kcal/oz or 80 kcal/100 mL.

Calcium and phosphorus are crucial to the development and maintenance of the human skeleton. In addition, calcium and phosphorus are integral components of many biochemical reactions. Calcium requirements are affected by protein and phosphorus intake in that these nutrients interact with the renal tubular reabsorption of calcium. Calcium-to-phosphorus weight ratios vary significantly for human milk (2:1) and cow milk (1.2:1). This ratio also varies in commercial infant formulas. Formulas designed for term infants will not meet the calcium and phosphorus needs of premature infants. For these infants, the additional calcium and phosphorus found in premature infant formulas is necessary for normal bone growth and mineralization. Typical amounts of calcium and phosphorus found in 20 kcal/oz infant formulas are 112–122 mg calcium/100 mL and 61–68 mg phosphorus/100 mL for preterm formulas versus 53–65 mg calcium/100 mL and 28–36 mg phosphorus/100 mL for term formulas. Human milk fed to premature infants requires calcium and phosphorus supplementation with either a human milk fortifier or addition of a transitional premature formula, as discussed later.

Nutrient-enriched transition or post-discharge formulas are designed specifically to provide for continued catch-up growth in premature infants after hospital discharge. Similac NeoSure and Enfamil EnfaCare (both milk-based formulas) contain MCTs as part of the fat source. The caloric (22 kcal/oz), protein, vitamin, and mineral contents of these formulas exceed those of standard term formulas but are less than those of 24 kcal/oz premature infant formulas. Use of these formulas in preterm infants until 9 months of postnatal age results in greater linear growth, weight gain, and bone mineral content than those achieved with the use of standard, term infant formulas.⁵⁹

Human Milk Fortifiers. Mothers who give birth to premature infants produce milk that is higher in protein, sodium, potassium, chloride, and iron, and possibly other nutrients than the milk of mothers who deliver at full term. However, these nutrients decline to the amounts found in mature human milk by 4–8 weeks after delivery. From 28 weeks' gestational age, the fetus receives 125–150 mg of calcium and 65–80 mg of phosphorus daily, with 80% being deposited in bone during this time. Without supplementation, human milk, whether preterm or mature, cannot supply the amounts of calcium and phosphorus needed to prevent osteopenia of prematurity. Human milk must

therefore be fortified for premature infants to achieve adequate growth.⁶⁰

Commercial products have been developed to supplement the nutrient content of human milk to meet the needs of most preterm infants. Enfamil Human Milk Fortifier Acidified Liquid, Similac Special Care 30, Similac Human Milk Fortifier Concentrated Liquid, Similac Human Milk Fortifier Hydrolyzed Protein Concentrated Liquid, and Prolact+ H²MF all are liquids that add nutrients to human milk without displacing a significant amount of volume. Enfamil Human Milk Fortifier Acidified Liquid, Similac Special Care 30, Similac Human Milk Fortifier Concentrated Liquid, and Similac Human Milk Fortifier Hydrolyzed Protein Concentrated Liquid are made from cow milk supplemented with whey protein to provide a whey/casein ratio of 60:40 and a fat mixture to provide MCTs. When added to human milk, fortifiers increase the osmolality by 85 mOsm/kg. Prolact+ H²MF is made from concentrated 100% human milk. It provides extra protein, calories, vitamins, and minerals and is specifically indicated for preterm infants weighing less than 1500 g. This product does not meet all nutritional goals, however, because it is human milk-based, necessitating added vitamin and mineral supplementation (e.g., vitamin D, iron). [Table 26–8](#) summarizes the composition of the human milk fortifiers. Studies support adequate weight gain and nutrient retention in infants when either fortified human milk or commercial preterm formulas are ingested.⁶¹ However, human milk has been shown to provide various immunologic benefits, as well as to improve the intelligence quotient (IQ) in infants born small for gestational age and very low-birth-weight infants.⁶² The use of these products will result in weight gain equivalent to that with intrauterine growth rates in most premature infants. Product selection will therefore be dictated by cost and clinical preference.

Table 26–8 Human Milk Fortifiers

Component	Enfamil Human Milk Fortifier Acidified Liquid^a	Similac Special Care^b	Similac Human Milk Fortifier Concentrated Liquid^c	Similac Human Milk Fortifier Hydrolyzed Protein Concentrated Liquid^c	Prolact+4 H²MF^d
Calories	30	61	7	7	28
Protein (g)	2.2	1.8	0.35	0.5	1.2

Component	Enfamil Human Milk Fortifier Acidified Liquid^a	Similac Special Care^b	Similac Human Milk Fortifier Concentrated Liquid^c	Similac Human Milk Fortifier Hydrolyzed Protein Concentrated Liquid^c	Prolact+4 H²MF^d
Fat (g)	2.3	4	0.27	0.21	1.8
Carbohydrates (g)	<1.2	4.7	0.81	0.75	1.8
Vitamin A (IU)	1160	761	197	197	61
Vitamin D (IU)	188	91.3	35	35	26
Vitamin E (IU)	5.6	2.4	1	1	0.4
Vitamin K (mcg)	5.7	7.3	2.4	2.4	<0.2
Thiamin (mcg)	184	152	48	48	4
Riboflavin (mcg)	260	377	123	74	15
Vitamin B ₆ (mcg)	140	152	49.4	50	4.1
Vitamin B ₁₂ (mcg)	0.64	0.33	0.08	0.13	0.05
Niacin (mg)	3.7	3	1.04	0.98	0.0524
Folic acid (mcg)	31	22.5	7	7	5.4
Pantothenic acid (mg)	0.92	1.2	0.309	0.31	0.0748
Biotin (mcg)	3.4	22.5	7.6	5.8	—
Vitamin C (mg)	15.2	22.5	7.71	7.7	<0.2
Calcium (mg)	116	109	35.1	30	103
Phosphorus	63	60.8	20	17	53.8

Component	Enfamil Human Milk Fortifier Acidified Liquid^a	Similac Special Care^b	Similac Human Milk Fortifier Concentrated Liquid^c	Similac Human Milk Fortifier Hydrolyzed Protein Concentrated Liquid^c	Prolact+4 H²MF^d
(mg)					
Magnesium (mg)	1.84	7.3	2.2	2.1	4.7
Iron (mg)	1.76	1.1	0.11	0.11	0.1
Zinc (mg)	0.96	0.9	0.30	0.31	0.7
Manganese (mcg)	10	7.3	2.1	2.2	<12
Copper (mcg)	60	152	15	15	64
Iodine (mcg)	–	3.7	0.5	0.4	–
Selenium (mcg)	–	1.2	0.204	0.2	–
Sodium (mg)	27	26.2	5.39	5	37
Potassium (mg)	45.2	78.5	21	21	50
Chloride (mg)	28	49.3	13.4	13	29

Note: Changes are made periodically in human milk fortifier composition; for the most up-to-date information, refer to the manufacturer's website.

^a Amount per 4 vials; generally mixed with 100 mL human milk to yield 120 mL, with a caloric density of 24 kcal/oz.

^b Amount per 60 mL; generally mixed with 60 mL human milk to yield 120 mL, with a caloric density of 25 kcal/oz.

^c Amount per 5 mL; 5 mL packet with 50 mL human milk to yield 55 mL, with a caloric density of 22 kcal/oz, or 5 mL packet with 25 mL human milk to yield 30 mL, with a caloric density of 24 kcal/oz.

^d Amount per 20 mL of Prolact + 4; generally mixed with 80 mL human milk to yield 100 mL, with a caloric density of 24 kcal/oz. Nutrient contribution from Prolact + 4 based on target values for macronutrients and minerals and on averages of three lots for vitamins.

Key: IU = International units.

Source: Abbott Nutrition (www.abbottnutrition.com); Mead Johnson Nutrition (www.meadjohnson.com); and Prolacta Bioscience (www.prolacta.com). Accessed October 26, 2019.

These products are expensive. Enfamil Human Milk Fortifier Acidified Liquid costs between \$2.56 and \$3.10 per vial (depending on purchasing as a case of 100 vials versus 200 vials), and one vial is generally added to each 25 mL of human milk to yield a 24 kcal/oz concentration. Moreover, this product comes only in cartons of 100 or 200 vials. Similac Special Care 30 costs as much as \$0.90 per ounce and, when added in equal parts (2 ounces of human milk to 2 ounces of Similac Special Care 30), yields a 25 kcal/oz concentration. Similac Human Milk Fortifier Concentrated Liquid and Similac Human Milk Fortifier Hydrolyzed Protein Concentrated Liquid both come in 5 mL packets, and addition of one packet to 50 mL of human milk yields a 22 kcal/oz concentration. When 5 mL is added to 25 mL of human milk, a 24 kcal/oz concentration is obtained. These two human milk fortifier products from Similac differ primarily in the amount of additional protein provided and cost approximately \$0.95/5 mL packet. They are sold in packages of 6 boxes of 24 packets each (total 144 packets). Prolact+ H²MF is the most expensive, at a cost of approximately \$6.25/mL, and the addition of 20 mL of Prolact+4 H²MF to 80 mL of human milk is required to yield a 24 kcal/oz concentration.

The strongest evidence supporting the financial benefit of human milk as a sole source of nutrition is in relation to decreased incidence of necrotizing enterocolitis.^{50,63} Once the infant is ready for discharge from the hospital or has reached a weight of 2.5 kg, one of the transition or post-discharge formulas can be added to human milk to increase the caloric density (1 teaspoon of powder added to 90 mL of formula yields 24 kcal/oz) and to promote delivery of other nutrients. Assessment of vitamin and mineral composition should be

determined before discharge to ensure that no further supplementation is required.

Metabolic Formulas. Infants with various inherited inborn errors of metabolism require specific formulas tailored to their particular condition and must be under the care of a specialist, usually a pediatric endocrinologist or geneticist. Information about these formulas is available on the various manufacturers' websites. These formulas, as well as formulas intended for use in low-birth-weight infants or in patients with specific medical conditions or dietary needs, are classified by FDA as exempt formulas—that is, exempt from FDA nutrient content and labeling requirements.⁶⁴

Concentrated Formulas. A child with caloric needs exceeding normal requirements may be given concentrated formula under medical supervision. A few ready-to-use formulas made from cow milk are available in a caloric density of 22 or 24 kcal/oz (Table 26–6). Various concentrations can be prepared from liquid concentrates or powders by varying the amount of water added (Tables 26–9 and 26–10). Increasing caloric density by adding less water also increases delivery of all nutrients, including protein and electrolytes, and decreases free water delivery. Increased concentration of protein and electrolytes (i.e., PRSL) in conjunction with decreased fluid intake may result in dehydration and electrolyte imbalances. Careful monitoring of the infant's fluid intake and output, weight, serum electrolytes, blood urea nitrogen, serum creatinine, and urine specific gravity and osmolality is recommended, especially on initiation of the concentrated formula.

Table 26–9 Dilution of Concentrated Liquid Infant Formulas^a

Caloric Concentration Desired (kcal/oz)	Liquid Formula Concentrate (oz)	Added Water (oz)
20	1	1
22 (actual 21.8)	3	2.5
24	3	2
26–27 (actual 26.7)	3	1.5
28–29 (actual 28.6)	5	2

^a Commercial concentrates of infant formula generally contain 40 kcal/oz before dilution with water.

Table 26–10 Dilution of Powdered Term Infant Formulas^a

Caloric Concentration Desired (kcal/oz)	Formula Powder (scoop)^b	Added Water (oz)
20	1	2
24	3	5
28	4	5.5
28	7	10.0

^a Powdered infant formulas generally contain 44 kcal per one level, unpacked scoop before dilution. If a large volume of formula is to be prepared, add powder necessary to supply desired calories; then add water to achieve the final volume desired. Directions for preparation may vary; check manufacturer's information.

^b Historically, the conversion of 1 scoop = 1 tablespoon of powder has been used. However, this scoop-equivalent measurement varies between powders. For improved accuracy, parents and caregivers should be instructed always to use the manufacturer's provided scoop for preparing formula products.

Modular macronutrient components ([Table 26–11](#)) can be added to either human milk or infant formula and are available as alternatives to concentrated formulas. Adding carbohydrates as glucose polymers can result in diarrhea. Protein supplementation may increase the PRSL. Fat may be added as MCTs (MCT Oil, Nestlé Nutrition; Liquigen, Nutricia) or Microlipid (Nestlé Nutrition) for infants with fat malabsorption or intolerance. Microlipid is an emulsion made from safflower oil that provides long-chain fatty acids and mixes well with formula. Addition of fat to milk or formula can lead to diarrhea, steatorrhea, delayed gastric emptying, vomiting, and gastroesophageal reflux. Adding modular components is more expensive and time-consuming than simply concentrating the formula; these components should be reserved for situations in which a single nutrient is needed or further concentration of the

formula is not appropriate.

Toddler Formulas. Toddler formulas (see under Older Infants/Toddler Milk-Based Formulas in [Table 26–6](#)) (e.g., Gerber Good Start Gentle 2, Go & Grow by Similac Toddler Drink, Enfagrow Toddler Transitions) are designed for infants and children 9–24 months of age. AAP, however, has stated that these formulas offer no nutritional advantages; standard formulas are appropriate for infants up to 12 months of age, and cow milk is appropriate for children 12 months of age and older.⁵¹

Table 26–11 Modular Additives

Additive^a(Mfr)	Nutrient(s) Provided	Amount of Nutrient(s)	Calories
Carbohydrate			
Polycal (Nut)	Maltodextrin	Per 5 g scoop: carbohydrate ~4.8 g	~20 kcal/ scoop
Protein			
Beneprotein (Nes)	Whey protein isolate (milk), soy lecithin	Per 7 g scoop or packet: protein 6 g	25 kcal/ scoop
Complete Amino Acid Mix ^b (Nutr)	Essential and nonessential amino acids ^c	4 g of protein in 5 g mix	3.16 kcal/g
Essential Amino Acid Mix ^b (Nutr)	Essential amino acids ^d	4 g of protein in 5 g mix	3.28 kcal/g
Liquid Protein Fortifier (A) (liquid)	Casein hydrolysate	0.17 g protein/ mL	0.67 kcal/ mL
Procel (GHP)	Whey protein concentrate (milk), soy lecithin	Per 6.6 g scoop: protein 5 g; fat 0.5 g	25 kcal/ scoop
ProMod Liquid Protein (A) (liquid)	Hydrolyzed beef collagen	0.33 g protein/ mL	3.3 kcal/ mL

Additive^a(Mfr)	Nutrient(s) Provided	Amount of Nutrient(s)	Calories
Fat			
Liquigen (Nut) (liquid)	MCTs (50%, palm kernel/coconut oils)	Per mL: fat 0.5 g	4.5 kcal/mL
MCT Oil (Nes) (liquid)	MCTs (coconut/palm kernel oils)	Per mL: fat 0.93 g	7.7 kcal/mL
Microlipid (Nes) (liquid)	Long-chain fats (safflower oil)	Per mL: fat 0.5 g	4.5 kcal/mL
Combined			
Benecalorie (Nes) (liquid)	Calcium caseinate (milk); high oleic sunflower oil, sucralose	Per 44 mL package: protein 7; fat 33 g	7.5 kcal/mL
Duocal (Nut)	Hydrolyzed cornstarch; blend of refined vegetable oils (corn, coconut), MCT (coconut/palm kernel oils)	Per scoop: carbohydrate 3.6 g; fat 1.1 g	25 kcal/scoop (5 g) 42 kcal/tablespoon
LiquaCal Liquid Protein (GHP) (liquid)	Hydrolyzed collagen protein, L-arginine, whey protein isolate, sucralose	Per 30 mL: carbohydrate 9 g; protein 16 g	3 kcal/mL

^a Products listed are powders unless specified otherwise.

^b Recommended mixing concentration of 5% w/v (5 g of powder to 100 mL of water)

^c Contains the following essential and nonessential amino acids: lysine, glutamate, leucine, arginine, proline, valine, aspartic acid, glycine, isoleucine, threonine, phenylalanine, histidine, serine, tyrosine, alanine, tryptophan, methionine, glutamine, and glutamic acid.

^d Contains the following essential amino acids: lysine, leucine, valine, threonine, isoleucine, tyrosine, phenylalanine, histidine, methionine, and tryptophan.

Key: A = Abbott Nutrition; GHP = Global Health Products; MCT = medium-chain triglycerides; Mfr = manufacturer; Nes = Nestlé Nutrition; Nut = Nutricia North America.

Source: Abbott Nutrition (www.abbottnutrition.com); Global Health Products

(globalhp.com); Nestlé Healthcare Nutrition (www.nestlehealthscience.us); and Nutricia North America (www.nutricia-na.com). Accessed October 26, 2019.

Formulas for Children 1–13 Years of Age. Nutritionally complete, isotonic, virtually lactose-free enteral formulas designed for young children who cannot tolerate a normal diet or eat solid food are available (see under Children's Formulas in [Table 26–6](#)) (e.g., PediaSure Enteral Formula, Nutren Junior, Boost Kid Essentials). Flavored products contain sucrose, have a pleasant taste, and can be used as oral supplements. These formulas also are appropriate to use as tube feedings regardless of delivery mode (e.g., gastric, duodenal, jejunal). They contain adequate amounts of calcium, phosphorus, iron, and vitamin D for this age group; the amounts contained in adult enteral products typically are inadequate.

Several therapeutic formulas also have been developed for children 1–13 years of age ([Table 26–6](#)). Peptamen Junior and PediaSure Peptide are peptide-based, semi-elemental formulas. Vivonex Pediatric, Neocate Junior, Neocate Splash (unflavored), and EleCare Jr are amino acid–based elemental formulas. These products are intended for use in children with altered digestive or absorptive capabilities caused by a number of conditions, including severe protein allergy and eosinophilic esophagitis ([Table 26–7](#)). Another area of infant feeding and nutrition of increasing popularity is home-prepared blenderized diets and whole food formulas (e.g., Kate Farms, PediaSure Harvest, Compleat Pediatric, Nourish, Liquid Hope). A discussion of these feeding modalities is beyond the scope of this chapter, however.

Nutritional Problems in Infancy

GI problems, especially diarrhea, can occur with the use of infant formulas, as well as with human milk or any food. Tooth decay and nutritional deficiencies are other potential problems.

Diarrhea

Diarrhea can lead to failure to thrive (with chronic diarrhea) and dehydration (with acute diarrhea). Infants are particularly susceptible to dehydration

because of their high metabolic rate and relatively higher ratio of surface area to weight and height. (See [Chapter 19](#) for information on dehydration.) Fluid depletion by diarrhea or vomiting may quickly (within 24 hours) produce severe dehydration with fluid and electrolyte imbalances, shock, and possible death. A potential formula-related cause of diarrhea and vomiting is the improper dilution of a concentrated liquid or powdered formula or the incorrect addition of a modular product.

If diarrhea develops, the pharmacist or other health care provider should ascertain the severity and duration, stool frequency, and formula preparation method. If the diarrhea appears to be severe (i.e., with many more stools per day than normal) or has continued for more than 72 hours, or if the infant is clinically ill (exhibiting fever, lethargy, anorexia, irritability, dry mucous membranes, or decreased urine output), referral for medical attention is warranted. (Diarrhea is discussed in [Chapter 16](#).)

Mild diarrhea will usually resolve without the need for medical intervention, but the infant should be observed closely for signs of dehydration. Temporarily discontinuing usual dietary intake is not recommended except during a 4- to 6-hour period of oral rehydration if the infant is dehydrated. Oral electrolyte replacement solutions manufactured especially for infants (e.g., Pedialyte, Enfamil Enfalyte) may be used for short-term replacement of fluid and electrolyte losses in mild to moderate dehydration to augment fluid intake, but these solutions should not replace formula or human milk intake.⁶⁵ Prevention of dehydration by replacement of ongoing losses with a glucose–electrolyte solution in liquid or frozen form is the best intervention for diarrhea in infants and children.

Lactose-free formulas or a lactose-free diet may be considered for infants and children with moderate to severe diarrheal illness, but full-strength lactose-containing formulas, human milk, or a regular diet can be used in most infants. Parents should be advised that diarrhea is likely to continue for 3–7 days regardless of the type of formula, and seeking medical consultation is warranted if a sudden increase in stool output occurs with resumption of feeding.⁶⁵

Other Gastrointestinal Issues

Adverse GI effects of formula include mechanical obstruction (from

inspissated milk curds) and hypersensitivity to specific milk protein. Cow milk intolerance is associated most often with an inability to digest lactose or milk proteins. Feeding hyperosmolar formulas may adversely affect premature infants during the early neonatal period and may be a contributing factor in the development of necrotizing enterocolitis. For this reason, initiation of feedings in these infants is most often done with unfortified human milk or a 20 kcal/oz premature infant formula. Typically, after the infant has reached an intake of 80–100 mL/kg/day of enteral feedings, the caloric density can be advanced, but one study suggests that earlier fortification at 20 mL/kg/day to improve the provision of protein is possible.^{54,66} Initiation and advancement of formula for premature infants should occur under medical supervision and do not constitute an appropriate strategy for self-care.

Tooth Decay

“Baby bottle” tooth decay can occur in children who are bottle-fed beyond the typical weaning period (1 year) and who go to sleep with a bottle. It also can occur if the infant is allowed to sip on a bottle or from a training cup frequently during the day. Caries can be seen in children younger than 2 years and may involve the maxillary incisors, maxillary and mandibular first molars, or maxillary and mandibular canines. Restorative dentistry is often required, with the potential for difficulty in speech development without prompt and appropriate repair. Methods for prevention once teeth start to erupt include substituting plain water for carbohydrate-containing formula or other drinks given in a bottle until the infant is weaned from the bottle, encouraging the use of a cup for high-sugar drinks such as juice, providing either infant juices that contain a higher proportion of water or standard juices diluted with additional water, ensuring adequate fluoride intake, and cleaning the baby’s mouth at least once daily.⁶⁷ Going to sleep with a bottle should be actively discouraged for all infants.

Nutritional Deficiencies or Toxicities

Generally, age- and condition-appropriate commercial infant formulas are nutritionally adequate and safe for most infants and children. Nutritional deficiencies reported historically with commercial infant formulas are unlikely today with appropriate supplementation procedures and technologic advances in processing.

Because of a concern about possible aluminum contamination of infant formulas, the Food and Agriculture Organization of the United Nations has identified a provisional tolerable aluminum intake of 1 mg/kg/day. Aluminum in toxic amounts can interfere with cellular and metabolic processes in the nervous system as well as negatively affect bone and liver tissue.⁶⁸ Aluminum toxicity is primarily a concern in patients with decreased or immature renal function, such as premature infants, and in those receiving intravenous therapies. If an infant were to ingest as much as 200 mL/kg/day of a formula known to have the highest aluminum content, the amount of aluminum received per day would still be less than 0.5 mg/kg/day. The highest aluminum concentrations in infant formulas (500–2400 mg/L) have been reported for soy protein–based formulas, because plants readily absorb aluminum from soil.

Infant Formula Preparation

Most formulas are available as a ready-to-use liquid or as a liquid concentrate or powder for reconstitution mixed with water. Ready-to-use formulas should *never* be diluted. They are convenient but usually more expensive. By contrast, concentrated liquids *must* be diluted, typically by mixing equal amounts of water and concentrated liquid (e.g., a 13-ounce can of formula with a 13-ounce can of water) to prepare a 20 kcal/oz formula ([Table 26–10](#)). Powdered term and preterm transition or post-discharge formulas provide a measuring scoop in the can and require addition of 1 unpacked, level scoop of powder to each 2 ounces of water for a 20 kcal/oz term formula and a 22 kcal/oz preterm post-discharge formula. Directions for preparation may vary between products, and the caregiver should always prepare the formula according to the manufacturer's or health care provider's directions. If parents or caregivers are given alternative directions from those printed on the can, these should be given in writing and explained thoroughly. Directions should be provided in the appropriate language for non–English-speaking parents. Before use, infant formula containers should be inspected for the expiration date and any damage. Unopened formula containers, cans, or bottles can be stored at room temperature but must not be subjected to extreme temperature changes.

Preparation Techniques

Each infant formula has specific instructions for preparation, and most formulas have symbols on the containers that can be used as guidelines for preparation. Because infants may be more susceptible to infection, various

sterilization methods have been recommended for preparation of formula for this age group. **Table 26–12** reviews sterilization methods for different types of formulas. Studies have shown that the “clean” method of preparing formula (i.e., without boiling the water) is as safe as terminal sterilization (i.e., boiling the water); therefore, some providers do not recommend boiling water. WHO and AAP currently recommend that all water for formula preparation be boiled, because of reports of municipal water supply contamination in some areas. If well or pond water is used or if the geographic watershed area is prone to flooding, the water must be boiled.^{69,70} If tap water is used, cold water should be run for at least 2 minutes before use to clear any lead or leached chemicals that might be in the pipes and thereby decrease toxin exposure. If bottled water is used in infant formula preparation, it should be treated the same as for tap or well water (i.e., it is boiled and cooled before use) unless the water is labeled as sterile.

Table 26–12 Sterilization Method for Infant Formula Preparation

General Preparation

- Always wash hands before preparing formula or handling bottles and nipples; repeat washing if interrupted.
- Sterilize bottles and other equipment (e.g., glass measuring cup, spoons, nipples, rings, disks) separately from the formula. Many pediatricians and other primary care providers now consider the use of a dishwasher with a heated drying cycle as adequate for sterilization of infant feeding supplies.
- Using tongs, place all equipment in a deep pan or sterilizer, cover all equipment with cold tap water, bring to a boil, and continue boiling for 5 minutes.
- Both tap water and bottled water should be heated until it reaches a rolling boil, allowed to continue to boil for 1–2 minutes, and then allowed to cool to room temperature for 30 minutes. Boiling for a longer period of time may concentrate impurities (e.g., lead) in the water.
- Using tongs, remove all items from the pan or sterilizer and place on a clean towel. Place bottles and nipples on the towel with their open ends facing down.

Concentrated Liquid Formula

- For cans, wash top of can with hot water and detergent, rinse in hot running water, and dry. Shake can well and open it with a clean punch-type can opener.
- For bottles, the protective cap must be removed. Shake bottle well and open.
- Mix appropriate amounts of concentrated liquid and sterilized water (according to product label or health care provider instructions). For accuracy, use a measuring cup for all measurements of formula and water.
- Pour formula into sterilized bottles; place nipples, rings, and disks on bottles.
- Tightly cover any unused formula and store in refrigerator. Use formula within 48 hours of

preparation or discard.

Powdered Formula

- Wash top of can with hot water and detergent, rinse in hot running water, and dry.
- Open can and mix appropriate amounts of powder and sterilized water (according to product label or health care provider instructions). For accuracy, use the scoop provided.
- Pour formula into sterilized bottles; place nipples, rings, and disks on the bottles.
- Tightly cover any unused prepared formula and store in the refrigerator. Use this formula within 24 hours of preparation.
- Cover any formula remaining in the can with the plastic top. Write the date on the opened can. Store in a cool, dry place for up to 1 month.

Ready-to-Use Formula

Ready-to-Use Cans

- Wash top of can with hot water and detergent, rinse in hot running water, and dry.
- Shake can well, and open it with a clean punch-type can opener.
- Add the amount of formula needed for a single feeding to one sterilized bottle or to the number of bottles needed for a full day's feedings.
- Do *not* add water.
- Prepared bottles and any formula left in the can should be tightly covered and refrigerated for up to 48 hours after the can was opened.

Ready-to-Use Bottles

- The protective cap must be removed, and a sterile nipple cap must be screwed onto the bottle before feeding.
- Shake each bottle well to ensure mixing of formula.

All Types of Formulas

- Warm bottle to desired temperature by immersing in hot water bath or holding under hot running water.
- Heating bottles in the microwave is not recommended owing to potential for creation of "hot" spots, which may burn the infant's mouth.
- Never boil or overheat formula.
- Shake each bottle well before feeding infant.
- Test formula temperature before feeding infant.
- After feeding, discard any formula left in bottle, and immediately rinse bottle and nipple in cool water.

^a If disposable bottle liners are used, only nipples, rings, and screw tops of bottles need to be sterilized; the bottle liners provided by the manufacturer are sterile.

Table 26–12 provides handling instructions and recommendations for storage of infant formulas once the original container has been opened. Expressed human milk should be stored in glass or plastic airtight containers, refrigerated, and used within 96 hours. Human milk can be frozen, preferably up to 6 months but as long as 12 months when the freezer's temperature is at least 0°F (–18°C) or colder, in accordance with CDC recommendations (https://www.cdc.gov/breastfeeding/recommendations/handling_breastmilk.htm). Frozen milk should be rapidly thawed by holding the container under tepid running water or placing it in a tepid water bath. Thawed human milk should always be used within 24 hours of thawing and never refrozen.

Adverse Effects of Improperly Prepared and/or Administered Formulas

As stated previously, failure to properly dilute a concentrated infant formula can result in a hypertonic solution with the potential for adverse effects of diarrhea and dehydration. In extreme cases, the ingestion of an overly concentrated formula can lead to hypernatremic dehydration (induced by water deficit), metabolic acidosis, and renal failure. Excessive formula dilution can lead to water intoxication, which can result in irritability, hyponatremia, coma, brain damage, or death. Such a situation may arise when a caregiver misunderstands the instructions for preparing a concentrated formula, dilutes a ready-to-use formula, or tries to make the baby's formula last longer by diluting it.

Parents or other caregivers may have questions about how much infant formula their child should receive. Typically, a health care provider at the hospital will have given parents feeding instructions before mother and infant are discharged home. When a formula change is made after hospital discharge, however, adequate information may not be provided in some health care settings. Generally, the required daily formula intake depends on the infant's age and weight and individual considerations such as the need for catch-up growth (**Table 26–13**). During the first year of life, a normal, healthy formula-fed term infant usually eats every 3–5 hours (average of 4 hours). Small or weak infants may eat every 2–3 hours, because they have smaller stomach capacity or shorter gastric emptying time, or tire easily during feedings.

Breastfed infants or those receiving human milk from a bottle also will nurse or eat more often, reflecting that human milk empties from the stomach more rapidly than formula.

Table 26–13 Average Age-Appropriate Number of Daily Feedings and Volume per Feeding

Age	Average Number of Daily Feedings	Average Volume per Feeding (oz)
Birth–2 weeks	6–10	2–3
2 weeks–1 month	6–8	3–5
1–3 months	5–6	4–6
3–4 months	4–5	6–7
4–12 months	3–5	7–8

Most term infants will tolerate longer intervals between feedings of up to 4 hours by the age of 3–4 weeks. Premature infants may continue to require frequent feedings past 6–8 weeks of age, depending on birth weight, corrected gestational age, and growth. Some infants begin to stop nighttime feedings after the age of 1–2 months, whereas others take as long as 4–6 months to cease such feedings. The process is highly variable and may depend more on weight attained than on a specific age; most infants are able to sleep through the night when they reach approximately 11 pounds.

The amount of formula offered to a bottle-fed infant should be consistent with the DRI for energy according to age and weight ([Table 26–2](#)). [Table 26–13](#) lists typical quantities of feedings for various age groups. The infant should be fed on demand and not forced to take more formula than is desired at any one feeding. If the infant finishes a bottle and still seems hungry, more formula should be offered. Parents also should be aware that a newborn typically loses weight (mostly water) during the first week of life, but by 2 weeks of age, the infant should be gaining weight. Healthy weight gain usually indicates that the infant is receiving an appropriate amount of formula. WHO standardized growth charts are used to determine whether an infant is growing appropriately. Weight, length/height, and head circumference should be determined at each medical visit.

Both underfeeding and overfeeding are potential problems. Infants who like to “graze” all day can take in too much milk and gain too much weight. However, this behavior also can be a sign of inadequate intake in breastfed infants, with consequent failure to thrive. Other problems associated with overfeeding are regurgitation, gastroesophageal reflux, vomiting, loose stools, constipation, and colic. Spitting up a small amount of formula, even after every feeding, is not usually a cause for concern. If the infant is regurgitating or vomiting significant amounts, a primary care provider should be consulted. Bilious emesis (with green-tinged vomitus) is always a reason for prompt medical evaluation.

Loose stools are normal for some infants, especially those receiving human milk or hydrolyzed formulas. A loose stool consistency also may be the result of an improperly concentrated formula or overfeeding. Rarely, loose stools may be the result of the administration of contaminated formula, as mentioned previously. The contaminated formula results in pathologic changes in the gut, leading to loose stools. Human milk-fed infants may have only 1 stool every 1–3 days; however, some infants will have 10–12 stools each day. Formula-fed infants usually have 1–3 stools per day. *Diarrhea*, defined as increased stool volume and frequency that differ from the usual volume and frequency, warrants medical attention when it persists for more than 3 days or when the infant appears dehydrated. Constipation is rare in human milk- or formula-fed infants; it most often results from inadequate formula (fluid) intake. Severe or prolonged constipation with straining and blood streaks on the stool warrants a visit to the primary care provider.

Product Selection Guidelines

For healthy term infants, a milk-based formula with or without added whey protein is indicated, except in patients who require a therapeutic formula. Recommendations for a formula should be based on ease of preparation or administration, the parent’s or caregiver’s ability to follow product directions, parental attitudes and preferences, availability of sanitary conditions and refrigeration facilities, and cost. Before assisting parents in selecting a therapeutic formula, the pharmacist should confirm that their primary care provider recommended its use.

For many parents, cost may be a critical factor in formula selection. Concentrated liquids and powders typically are less expensive than ready-to-

use products. Convenience also is a consideration. The preparation of powdered and concentrated liquid formulas requires more manipulative functions and more attention to clean technique. The formula selected should be one that is well tolerated by the infant, convenient for parents and caregivers, and priced to fit the family's budget. To simplify formula preparation away from home, parents can select products available in unit-of-use packaging for ready-to-use liquids, or they can place a powder packet or powder in an empty bottle and add water whenever needed.

The federal grant program Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) helps ensure that all infants, children (up to 5 years of age), and pregnant, postpartum, and breastfeeding women have access to adequate nutrition. State health departments and other agencies regulate and allocate funds in the federal grant program (i.e., approximately \$5.4 billion in fiscal year 2018). Formula and preventive services are subsidized for eligible participants but often require a prescription and previous authorization. More than 6.8 million persons received WIC benefits each month in 2018, most of them infants and children.⁷¹

Vitamin and Mineral Supplementation

Routine multivitamin and mineral supplementation generally is unnecessary for most formula- or human milk-fed term infants. However, some infants may be at risk for deficiency and require appropriate supplementation. Cases of vitamin D-deficiency rickets continue to be reported in the United States, and the prevalence of iron-deficiency anemia among children 1–3 years of age is 2.1% in the general population.^{52,72} Accordingly, particular care is warranted to ensure that children in this age group get adequate dietary iron. AAP does not, however, endorse routine iron supplementation in children 1–3 years of age unless the child's diet is low in iron-containing foods.⁵² With likelihood of deficiency or recognition of risk factors, the child should be referred to the family's regular health care provider for further evaluation.

Vitamin and mineral supplementation may be needed for preterm and human milk-fed infants whose nutrition is inadequate^{73–75} (Table 26–14). These infants and those with other nutritional deficiencies, malabsorptive and other chronic diseases, rare vitamin-dependent conditions, inborn errors of vitamin or mineral metabolism, or deficiencies related to the intake of certain medications will need a medically supervised regimen of vitamin and mineral

supplementation.

Table 26–14 Guidelines for Use of Vitamin and Mineral Supplements in Healthy Infants^a					
Age Group	Multivitamin/Mineral	Vitamin D^b	Vitamin E	Folate	Iron^c
Full-Term Infants					
Human milk-fed	0	+	0	0	±
Formula-fed	0	± ^d	0	0	0
Preterm Infants					
Human milk-fed ^e	+	+	0	0	+
Formula-fed ^e	+	+	0	0	+
Older Infants (>6 Months)					
Normal	0	0	0	0	±
High-risk ^f	+	0	0	0	±

^a Not shown is vitamin K for newborn infants and fluoride in areas with insufficient fluoride in drinking water supply ([Table 26–15](#)).

^b All infants should have a minimum daily intake of 400 international units of vitamin D beginning during the first few days of life; this intake should be continued throughout childhood and adolescence.

^c Iron-fortified formula and infant cereals are more convenient and reliable sources of iron than a supplement.

^d Supplement typically is indicated if infant is receiving less than 1000 mL daily of formula. An exception is Enfamil Premium Newborn, which is indicated for use from birth to the age of 3 months and provides 400 international units of vitamin D in 810 mL (27 fluid ounces).

^e Multivitamin supplements (plus added folate) are needed primarily when calorie intake is below approximately 300 kcal daily or when the infant weighs less than 2.5 kg; vitamin D should be supplied at least until the age of 6 months in human milk-fed infants. Iron should be started by the age of 2 months.

^f Multivitamin/mineral preparations including iron are preferred to supplements containing iron alone.

Key: + = Supplement usually indicated; ± = supplement sometimes indicated; 0 = supplement not usually indicated.

Source: [References 10](#) and [73–75](#).

Human Milk–Fed, Full-Term Infants

The healthy, full-term, human milk–fed infant requires little to no special supplementation for the first 4–6 months of life except for vitamin D and iron. AAP recommends vitamin D supplementation (400 international units per day) for all human milk–fed infants unless they are weaned to at least 1000 mL daily of vitamin D–fortified formula. Risk factors for vitamin D deficiency include higher birth order (third child or later), dark skin, cultural or sociogeographic factors that minimize maternal skin exposure to sunlight, and delayed intake of dairy products in the infant or mother because of intolerance or other factors.⁷⁶ Mothers should be encouraged to maintain a balanced diet and to drink 3–5 8-ounce glasses of milk each day while breastfeeding. If the mother cannot tolerate milk because of lactose intolerance, lactose digestion aids (e.g., Lactaid, Dairy Ease, various store brands) and lactose-free milk are available. Mothers who do not drink milk should be encouraged to increase vitamin D and calcium intake through other dietary sources or by taking supplements. Furthermore, if the infant is showing signs or symptoms of being excessively colicky, the primary care provider should consider a “milk” sensitivity. If sensitivity is confirmed, the breastfeeding mother should decrease her dairy consumption and seek nondairy sources of calcium and vitamin D. Some primary care providers recommend complete removal of dairy products from the diet, whereas others suggest a more moderate approach that allows better-tolerated foods such as yogurt and cottage cheese.

Human milk–fed infants rarely develop iron-deficiency anemia before the age of 4–6 months.⁵² Although the iron concentration in human milk averages only 0.3–0.5 mg/L, the form of iron present is well absorbed. At the age of 4–6 months and beyond, the iron stores in infants fed human milk exclusively may become exhausted, necessitating a supplemental source. The addition of iron-

enriched foods such as fortified infant cereals will usually meet needs, or alternatively, an iron supplement (as elemental iron at a dosage of 1 mg/kg/day) can be given.⁵² However, one study reported an association between increased duration of breastfeeding and decreased iron stores in the body.⁷⁷ Term infants who are small for gestational age are likely to have higher requirements, but the necessity for supplementation in this population is unclear.

The first iron-enriched food introduced into the infant's diet typically is infant cereal. Bioavailability of the large-particle, electrolytic iron powder used to fortify dry infant cereals is substantially less than that of ferrous sulfate iron used in milk- or soy protein-based formulas. Cereals also contain potent inhibitors of iron absorption and constitute an unreliable source of iron sufficient to prevent deficiency for infants who receive minimal iron from other sources. With iron-fortified, wet-packed cereal and fruit combinations marketed in jars, the ferrous sulfate is not exposed to oxygen until the jar is opened; therefore, iron absorption is improved. Consuming fruit juices and other products containing ascorbic acid along with iron-fortified cereals has been shown to enhance iron absorption.⁷⁸

Formula-Fed, Full-Term Infants

Full-term infants who consume adequate amounts of an iron-fortified, milk-based formula do not need vitamin and mineral supplementation in the first 6 months of life. An iron-fortified formula is preferred to ensure adequate iron stores for growing infants. Infants fed iron-fortified formulas do not demonstrate a difference in stool consistency, fussiness, colic, or regurgitation compared with infants fed low-iron formulas. Vitamin and mineral supplements are not needed for infants older than 6 months who receive a diet consisting of formula and increasing amounts of infant and table foods. A multivitamin with minerals may be needed, however, if the infant is at special nutritional risk secondary to a metabolic syndrome or other medical condition.

Preterm Infants

Preterm infants fed with either human milk or formula need vitamin and mineral supplementation. Their nutrient needs are greater than those of full-term infants because of their more rapid growth rate, relative inability to ingest an adequate volume of formula or human milk, decreased intestinal

absorption, and lower body stores. Premature infants often require a multivitamin supplement to provide the equivalent of the recommended intakes for full-term infants while receiving maternal breast milk, inadequate daily volume totals (less than 1000 mL daily), or certain formulas (e.g., Similac Alimentum), or before reaching a body weight of 2.5 kg.

Premature infants are especially susceptible to iron-deficiency anemia because of their marginal iron stores at birth. Without iron supplementation or blood transfusions given for clinically significant low hemoglobin/hematocrit, iron stores will be depleted by the age of 2 months, in contrast with depletion at 4–6 months in full-term infants.

Originally the AAP-CON recommendations included supplementation with elemental iron at a dosage of 2 mg/kg daily for premature infants with birth weights between 1500 and 2500 g once they were 2 months old or had doubled their birth weight.^{52,59} AAP currently recommends that preterm infants who receive human milk should receive elemental iron supplementation (2 mg of elemental iron/kg/day minimum, with up to 4–6 mg of elemental iron/kg/day in cases of deficiency) earlier, within 1 month, through 12 months of age. If these preterm infants are switched from human milk to formula, they will most likely not require iron supplementation once they are consuming 150 mL/kg/day. However, reports have shown that approximately 14% of preterm infants receiving appropriate formula will still need a supplement at 4–8 months of age because of decreased iron stores.⁵² To address this deficit, some clinicians advocate even earlier initiation of iron supplementation in preterm infants born at less than 30 weeks of gestational age by starting supplementation as early as 2 weeks of chronologic age with elemental iron doses of 2–4 mg/kg/day.⁷⁹ Infants receiving erythropoietin should receive elemental iron 6 mg/kg daily. To minimize the possibility of hemolytic anemia related to insufficient vitamin E absorption, iron supplements should be withheld until the preterm infant is 2 weeks old. However, with adequate vitamin E supplementation in the formula, the risk of hemolytic anemia is minimal.

Supplementation of calcium, phosphorus, and vitamin D in preterm infant formulas is necessary to ensure adequate bone mineralization and to prevent osteopenia and rickets. The prevention of severe bone disease in preterm infants appears to depend on both high oral intakes of calcium and phosphorus and the intake of at least 400 international units (12.5 mg) of

vitamin D per day.⁵⁹ Therefore, preterm infants should receive specialized formulas, tailored to their needs, containing appropriate amounts of calcium, phosphorus, and vitamin D. Depending on the volume of formula consumed, vitamin D supplementation may be necessary, along with a premature formula, to provide 400–800 international units daily. Additionally, if patients are receiving either furosemide for congestive heart failure or bronchopulmonary dysplasia or phenobarbital for seizure disorders, increased vitamin D supplementation may be required.⁸⁰

Fluoride Supplementation

When used appropriately, fluoride is both safe and effective in preventing and controlling dental caries. Fluoride helps prevent dental decay by reducing the solubility of enamel, limiting the ability of bacteria to produce acid, and promoting remineralization. Systemic fluoride, such as that obtained from fluoridated water, primarily provides a topical benefit to teeth: Fluoride is secreted from the salivary glands, for near-constant contact with tooth surfaces.⁸¹ In 2014, CDC reported that 75% of the U.S. population for whom the water supply comes from a fluoridated community water system receive adequate fluoride.⁸²

Fluoride supplementation currently is not recommended from birth to the age of 6 months. Furthermore, the recommended supplementation for children 6 months to 16 years of age whose drinking water is inadequately fluoridated and who do not receive adequate fluoride from other sources has been decreased from previous recommendations because of an increased incidence of fluorosis.⁸³ Fluorosis, which affects approximately 22% of U.S. children, is manifested in the dentition as changes ranging from minor white lines running across the teeth to a very chalky appearance resulting from too much fluoride. Infants who are being fed powdered or concentrated formula should be given fluoride supplements only if the community's drinking water, or bottled water used for making formula, contains less than 0.3 ppm of fluoride. Bottled water often is free of fluoride, and its use for reconstituting formula mandates appropriate supplementation. **Table 26–15** can be used to determine the proper fluoride supplementation for a child, depending on the fluoride level in the drinking water. Ready-to-use formulas are manufactured with defluoridated water and contain less than 0.3 ppm of fluoride. The primary care provider may recommend a fluoride supplement for infants not receiving adequate fluoride.

Table 26–15 Recommended Fluoride Supplementation

	Daily Supplementation (mg)^a Indicated for Fluoride Concentration in Drinking Water		
Age Group	<10.3 ppm	0.3–0.6 ppm	>0.6 ppm
Birth–6 months	0	0	0
6 months– 3 years	0.25	0	0
3–6 years	0.50	0.25	0
6–16 years	1.00	0.50	0

^a Sodium fluoride 2.2 mg contains fluoride 1 mg.

Source: [References 76, 77, 81, and 83](#); and Rozier RG, Adair S, Graham F, et al. Evidence-based clinical recommendations on the prescription of dietary fluoride supplements for caries prevention. *J Am Dent Assoc.* 2010;141(12):1480–1489. Available at: [http://jada.ada.org/article/S0002-8177\(14\)60477-3/pdf](http://jada.ada.org/article/S0002-8177(14)60477-3/pdf). Accessed October 27, 2019.

Assessment of Infant Nutrition: A Case-Based Approach

Body weight, length (height), and head circumference are the growth parameters for determining whether infants are receiving appropriate nutrients, are digesting and absorbing ingested nutrients, or both. If an infant appears to be underweight or underdeveloped, the pharmacist should advise the parent that further medical evaluation is warranted.

The pharmacist's primary role in infant nutrition is to provide information about breastfeeding and infant formula products, including assistance with product selection and preparation instructions.

Cases 26–1 and 26–2 are examples of assessment of infant nutrition in two different patients.

Case 26–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	A mother is worried about her 4-week-old daughter spitting up formula after every feeding, almost always with a little force. Although some emesis has occurred since birth, the amount and frequency have increased over the past few days. The mother thinks her daughter seems colicky, often crying from "gas pains." The infant has always been a "good burper," so her mother feels that the gas pains are not related to too much air in the stomach. The infant appears to be well hydrated, and according to her mother, she has no fever.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Emesis occurs only after feedings. The infant appears to be more comfortable after each episode of emesis. Irritability associated with gas pains appears to be relieved by simethicone.
c. Description of the patient's efforts to relieve the symptoms	The mother has been giving the infant simethicone for gas. Nothing specific has been done for the emesis.
d. Patient's identity	Lydia Smith

e. Patient's age, gender, length/height, and weight	4 weeks, female, 21.5 in., 10 lb 9 oz (4.8 kg)
f. Patient's dietary habits	Lydia was receiving primarily breast milk until 7 days ago, when her mother switched her to formula because of inadequate breast milk supply. The infant's feedings were changed to Similac Advance. Per Mrs. Smith's report, the formula is being mixed to a standard 20 kcal/oz concentration according to the instructions on the container. The infant takes approximately 165 mL (5.5 ounces) every 3 hours. No extra water or juice is given during the day.
g. Patient's sleep habits	Lydia has not yet started sleeping through the night.
h. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Lydia is a healthy term infant without any significant medical conditions or past medical history. Her mother is currently giving her simethicone 20 mg up to 4 times a day as needed for apparent gas pains. She says that she usually gives approximately 2-3 doses per day.
i. Allergies	NKA
j. History of other adverse reactions to medications	None
k. Other (describe) -----	n/a
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary	<i>Primary problem:</i> emesis with feedings
	<i>Secondary problem:</i> increased intestinal gas

problem(s).	
3. Identify exclusions for self-treatment.	Bloody or bilious emesis
	Signs of dehydration: sunken fontanelle, dry mucous membranes, decreased number of wet diapers, dark urine, decreased oral intake
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required and share this information with the patient or caregiver.	Options include (1) Refer Lydia for immediate medical attention/PCP management. (2) Review preparation of infant formula with Mrs. Smith. (3) Monitor Lydia's symptoms and recommend nondrug measures only. (4) Recommend a medication alone or combined with nondrug measures. (5) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient/caregiver preferences.	Lydia's current feeding schedule, 165 mL of 20 kcal/oz of formula every 3 hours, provides 183 kcal/kg/day in a volume of 275 mL/kg/day. Both exceed the usual recommended intakes for a healthy term newborn (Tables 26-2 and 26-12). Because the emesis and gas pain have increased since Lydia's transition from breast milk to infant formula, Lydia most likely is not tolerating the volume of the formula provided every 3 hours. Unlike when Lydia was breastfed, the formula provided in a bottle can be visually seen by the caregiver, and the infant is often encouraged to complete ingestion of the bottle contents. If the caregiver is providing an excessive volume of formula, the infant may consume the entire volume but may regurgitate the additional quantity owing to a much smaller tolerated gastric volume. In addition to limiting the volume of formula, use of a slow-flow nipple to regulate the flow of milk may be of benefit. Explain to Mrs. Smith the correlation between the increased emesis and volume of formula provided. Also describe how she can assess the appropriateness of the volume fed to Lydia by appropriate weight gain and Lydia's satisfaction

	when full. Remind her not to feed Lydia beyond what she desires. Recommend that Mrs. Smith contact Lydia's PCP to discuss appropriate advancement of infant formula as she grows. If Lydia continues to have problems after a change in volume, her mother should follow up with her PCP for further management.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Simethicone should be stopped. The increased emesis and gas pain are caused by an excessive volume of formula provided every 3 hours. Providing a smaller volume of infant formula at each feeding should relieve Lydia's symptoms. If the symptoms persist after the change in volume, Lydia should be seen again by her pediatrician or other primary care provider."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Because the symptoms started (or acutely worsened) with the change from breast milk to infant formula and the caloric density but not the volume of the infant formula is appropriate for a healthy term infant, excessive volume of formula at each feeding is the most likely cause of Lydia's emesis and irritability. If the volume is the major issue, changing the volume should produce relief of symptoms within several days."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
a. Product storage requirements	"Infant formula should be used soon after mixing or kept tightly covered in the refrigerator and used within 24 hours of preparation. If the infant has already consumed some of the formula out of the bottle, the rest should either be consumed within 1 hour or discarded. See the product information insert for any specific storage requirements."

b. Specific nondrug measures	n/a
Solicit follow-up questions from the patient or caregiver.	"What if Lydia continues to have emesis and gas pain after seeing the primary care provider and decreasing the volume of formula provided?"
Answer the patient's or caregiver's questions.	"From the history, it sounds like Lydia might be receiving too much formula at each feeding. If she receives less volume at each feeding, her emesis and gas pains should noticeably lessen. If a change in volume does not help relieve her symptoms, her primary care provider will further assess her gastrointestinal intolerance."
Follow-up: Evaluate and Monitor	
9. Assess patient outcome.	Ask Mrs. Smith to call in 2-3 days to update you on Lydia's response to your recommendations, or you could call her in a few days to evaluate the response. If no improvement has occurred, ensure that she has made an appointment with Lydia's PCP for further evaluation.

Key: GI = Gastrointestinal; n/a = not applicable; NKA = no known allergies; PCP = primary care provider.

Case 26-2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and	

medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The mother of a healthy-appearing 4-month-old term infant comes to the pharmacy for advice on whether she should start to give him vitamins, because he is exclusively breastfed. His pediatrician suggested this at his recent well child checkup. The mother asks specifically if she should have her child take the multivitamin Poly-Vi-Flor, which her friend's 11-month-old son takes, because he is still breastfeeding.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	None
c. Description of the patient's efforts to relieve the symptoms	n/a
d. Patient's identity	Aaron Adams
e. Patient's age, gender, length/height, and weight	4 months (born at 40 weeks' gestational age), male, 24.5 in., 15 lb 13.5 oz (7.2 kg)
f. Patient's occupation	n/a
g. Patient's dietary habits	Mrs. Adams is still on maternity leave. Aaron is exclusively breastfed, eating approximately every 3–4 hours during the day.
h. Patient's sleep habits	He sleeps from 10 pm to 6 am.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Aaron is a healthy term infant with no preexisting medical conditions. He currently takes no prescription or nonprescription medications and no dietary supplements.
j. Allergies	NKA
k. History of other adverse reactions to medications	None

1. Other (describe) -----	n/a
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Potential for vitamin D and iron deficiency due to age and exclusive breast milk diet. No current need exists for fluoride supplementation, because the patient is younger than 6 months of age.
3. Identify exclusions for self-treatment.	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer this patient to the PCP. (2) Recommend a nonprescription multivitamin with iron but without fluoride supplementation. (3) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient/caregiver preferences.	Recommend a standard infant multivitamin containing ferrous sulfate.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Your primary care provider suggested a multivitamin, because Aaron is now 4 months of age and is exclusively breastfed. I would recommend a standard infant multivitamin containing iron as ferrous sulfate."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Term infants have approximately a 4- to 6-month store of iron reserves in their bodies. Human milk is very low in iron but meets most infants' needs for the first 4-6 months. However, Aaron's need for adequate vitamin D currently exceeds the amount provided in breast milk. Aaron is younger than 6 months old, so he currently does not require fluoride supplementation, which is present in Poly-Vi-Flor. For these reasons, your primary care

	provider suggested you start giving a daily multivitamin containing iron, not fluoride.”
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
a. Appropriate dose and frequency of administration	“Give Aaron an infant multivitamin with iron (e.g., Enfamil Poly-Vi-Sol with Iron Drops) 1 mL by mouth daily.”
b. Maximum number of days the therapy should be employed	“Until recommended to discontinue per Aaron’s pediatrician or regular health care provider.”
c. Product administration procedures	“Measure liquid using the dropper that comes with the medication and have Aaron swallow the liquid.”
d. Expected time to onset of relief	n/a
e. Degree of relief that can be reasonably expected	n/a
f. Most common adverse effects	“Adverse effects are rare, but gastrointestinal symptoms are possible. Give the iron drops with food if these effects occur.”
g. Adverse effects that warrant medical attention	“Contact a health care provider if signs of an allergic reaction, such as a rash or trouble breathing, occur after a dose is given.”
h. Patient’s/caregiver’s options in the event that condition worsens or persists	n/a
i. Product storage	“Keep all medications in a tightly secured container away from any

requirements	extreme temperature and out of children's reach."
j. Specific nondrug measures	n/a
Solicit follow-up questions from the patient or caregiver.	"What do I do if Aaron spits out a dose of the multivitamin product?"
Answer the patient's or caregiver's questions.	"If Aaron spits out a dose of the multivitamin product, do not try to give the dose again. The medication is not so vital that it must be given each day for a medical condition, and Aaron could potentially receive too much iron if he is given multiple doses. Be aware of the potential for the multivitamin product to stain clothing."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Ask Mrs. Adams to call after 1 week with an update on her son's response to your recommendations, or you could call her in a week to evaluate Aaron's response.

Key: n/a = Not applicable; NKA = no known allergies; PCP = primary care provider.

Patient Counseling for Infant Nutrition

The number and variety of infant formulas available may bewilder some parents. Once the formula type recommended or prescribed by the baby's primary care provider is known, the parents can be directed to an appropriate product. If the parents need further assistance with product selection, the pharmacist can make a recommendation to accommodate their preferences. At these encounters, the parents should demonstrate that they know how to properly prepare their baby's formula and how much formula to give at each feeding. The box "Patient Education for Infant Nutrition" lists specific information to include in patient counseling for parents and caregivers. In addition, families who may qualify for the WIC program but are not enrolled can be advised of its availability and benefits.

Patient Education for Infant Nutrition

Optimal nutrition is critical in infants and children to ensure normal growth and development. Parents who carefully follow product instructions for formula preparation and the measures listed here will help ensure optimal nutrition-related outcomes.

- Check unopened formula containers for damage. Do not use products if the container is significantly dented or if the expiration date has passed.
- When preparing formula from powder or liquid concentrate, carefully follow instructions for dilution to the desired caloric density ([Tables 26–8](#) and [26–9](#)). If the formula is too concentrated, the baby may have diarrhea or become dehydrated. If it is too dilute, the baby can become water-intoxicated, which can lead to irritability, seizures, coma, or brain damage.
- When preparing formula from powder or liquid concentrate, follow the technique for aseptic processing and sterilization. Be sure to sterilize the bottles (or use sterile liners) and other equipment, and boil the water used to make the formula ([Table 26–11](#)).
- When preparing ready-to-use formulas, do not add water to the formula. Follow the instructions in [Table 26–11](#). Be sure to sterilize the bottles (or use sterile liners) and other equipment.
- Use prepared or opened ready-to-use formula within 48 hours. Keep refrigerated.
- Feed your baby according to the frequency and quantities listed in [Table 26–12](#) unless instructed otherwise by the baby's primary care provider. Paying careful attention to your infant's hunger and fullness cues is important to avoid over- and underfeeding. Discuss any concerns with your infant's primary care provider.
- Heating formula in a microwave is not recommended. However, if formula or human milk is warmed in a microwave, follow these instructions to prevent a container explosion incident or scalds or burns to the baby's mouth:
 - Remove the bottle's lid to allow heat to escape.

- Heat only 4 ounces or more of refrigerated milk; do not thaw frozen human milk in a microwave. Place frozen human milk in a tepid water bath to thaw.
- Heat 4 ounces of refrigerated formula on full power for no longer than 30 seconds; heat 8 ounces of refrigerated formula for 45 seconds.
- After heating the formula, replace the nipple assembly and invert the bottle a minimum of 10 times.
- Test the formula's temperature by putting a few drops on your tongue or the top part of your hand or the underside of the wrist. Do not feed the baby the formula unless it feels cool to the touch.

When to Seek Medical Attention

- Seek medical attention if
 - Your baby is regurgitating or vomiting significant amounts of formula. A small amount of spitting up is normal. Projectile vomiting or bilious emesis (with green-tinged vomitus) always warrants immediate medical attention.
 - Your baby has severe diarrhea or diarrhea that persists for more than 3 days.
 - Your baby appears dehydrated (e.g., decreased number of wet diapers, dark urine, limp body tone, no tears, lethargic appearance).
 - Your baby's stools have blood in them.

Key Points for Infant Nutrition and Special Nutritional Needs of Children

- Human milk is the optimal food for infants younger than 12 months of age, and its use should be encouraged for nearly all infants. When breastfeeding or provision of human milk is not possible or desired, commercial infant formulas provide a safe,

nutritionally adequate substitute.

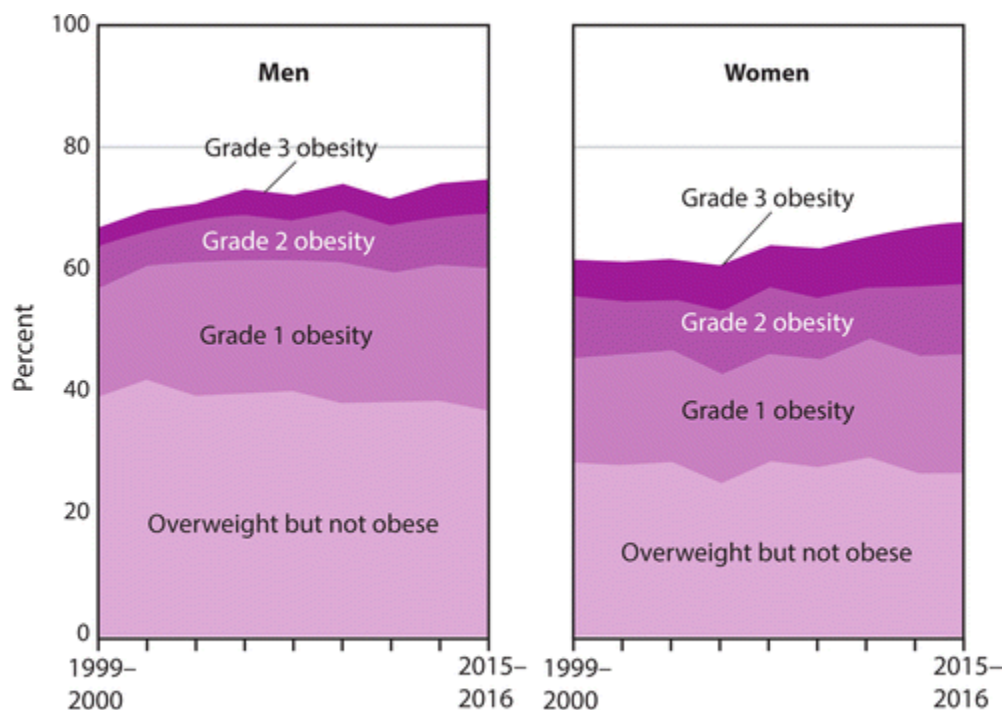
- Commercial formulas are available in a variety of types to meet the needs of most infants, as well as children with special nutritional requirements, such as for a feeding tube.
- Therapeutic formulas designed for infants and children with altered requirements dictated by disease or other conditions, including prematurity, vary in content and are not generically equivalent. These formulas should be used under medical supervision and are not self-selected.
- Accurate preparation of formula is critical to ensure optimal nutritional outcomes. Parents and caregivers should be counseled on proper preparation techniques.
- Some infants will require vitamin and/or mineral supplementation when their needs are not adequately met by their formula intake.
- Parents should be referred to their regular health care provider if the child has persistent vomiting or if at any time the emesis fluid is bilious (green-tinged).
- Parents should be referred to an appropriate health care provider if the child has diarrhea lasting more than 3 days, especially if dehydration develops, if the child looks clinically ill, or if blood is present in the stool.

Chapter 27: Overweight and Obesity

Authors: Sarah J. Miller, Sherrill Brown

Obesity rates in the United States have increased dramatically since the mid-1970s. Overweight and obesity are significant health factors because they are associated with increased morbidity from various conditions, including cardiovascular disease (CVD), type 2 diabetes, gallbladder disease, osteoarthritis, and several cancers.¹

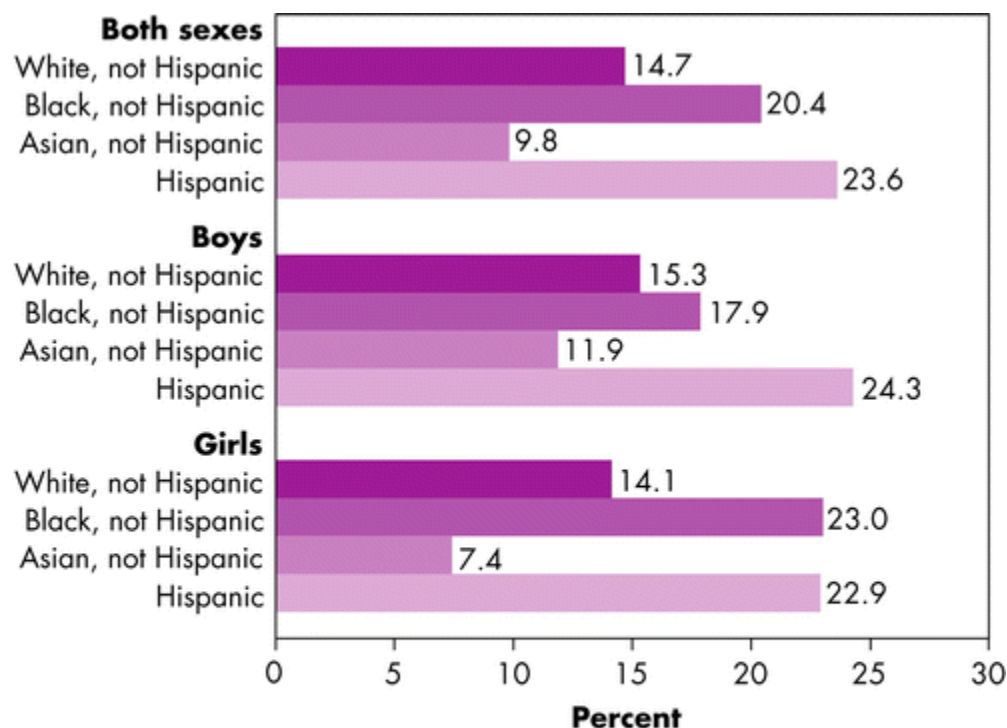
The National Health and Nutrition Examination Survey (NHANES) studies of the U.S. population have tracked prevalence rates for overweight and obesity in adults from 1960 to the present. NHANES data have demonstrated a marked increase in obesity in both men and women across all age and ethnic groups. As of 2016, nearly 40% of U.S. adults were obese ([Figure 27-1](#)), and more than 70% were either overweight or obese.² In the same dataset, prevalence of overweight remained more stable over time compared with the rising prevalence of obesity.² More males than females fell into the overweight but not obese category, whereas more females than males were obese.²



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Figure 27-1 Overweight and obesity among adults. (Source: [Reference 2.](#))

Prevalence of obesity during childhood and adolescence also is a public health concern ([Figure 27-2](#)).³ NHANES data for 2013–2016 show obesity in 18% of youths 2–19 years of age; the prevalence was much lower at 5%–7% in the 1960s.³ Obese children, especially those in adolescence, are likely to enter adulthood still exhibiting obesity and are at increased risk for developing chronic conditions such as diabetes mellitus and cardiovascular disease at earlier ages.



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Figure 27-2 Obesity among children and adolescents aged 2–19 years, by sex and race and Hispanic origin: United States 2013–2016. (Source: [Reference 3](#).)

The economic impact of overweight and obesity is substantial. The Milken Institute estimates that in the United States in 2016, obesity-related chronic diseases accounted for nearly half a trillion dollars in direct health care costs.⁴ In further estimates, obesity was responsible for more than \$1.2 trillion in productivity costs. Quantification of costs that are directly due to obesity is difficult, because many comorbid conditions associated with obesity have other possible causes.

Americans spend billions of dollars on weight control products and services

annually. Use of nonprescription or dietary supplement weight loss products is common. For maximum effectiveness in counseling patients with weight loss concerns, today’s pharmacists as health care providers need to be knowledgeable regarding benefits as well as limitations and potential harm of weight loss products, and they should be comfortable in recommending appropriate nonpharmacologic lifestyle changes, such as diet and exercise. Patients who need additional strategies can be referred for medical evaluation; considerations may include prescription weight loss therapies, weight loss devices, and weight loss surgery.

Clinical Indicators of Overweight and Obesity

The 2013 systematic review *Managing Overweight and Obesity in Adults*, prepared by the U.S. Department of Health and Human Services (USDHHS), defines overweight and obesity in adults by *body mass index* (BMI), a parameter that takes into account both height and weight.¹ BMI is calculated by dividing body weight in kilograms by height in meters, squared (kg/m²). The U.S. Preventive Services Task Force (USPSTF) on screening for and management of obesity also recommends the use of BMI for screening of obesity.⁵[Table 27–1](#) shows BMI values for persons of various heights and weights and also provides formulas for calculation of BMI. *Overweight* is defined in adults as a BMI of 25–29.9, which corresponds with Grade 1 overweight, and *obesity* as a BMI of 30 or greater. Severe or morbid obesity refers to a BMI greater than 40, corresponding with Grade 3 overweight; BMI between 30 and 40 accords with Grade 2 overweight.

Table 27–1 BMI Corresponding to Height and Body Weight^a

Table 27–1 BMI Corresponding to Height and Body Weight^a

BMI^{b,c}

	19	20	21	22	23	24	25	26	27	28	29	30	35	40
Height (inches)	19	20	21	22	23	24	25	26	27	28	29	30	35	40
Height (inches)	Body Weight (pounds)													
58	91	96	100	105	110	115	119	124	129	134	138	143	167	191
59	94	99	104	109	114	119	124	128	133	138	143	148	173	198
60	97	102	107	112	118	123	128	133	138	143	148	153	179	204

BMI ^{b,c)}														
	19	20	21	22	23	24	25	26	27	28	29	30	35	40
Height (inches)	Body Weight (pounds)													
60	190	198	107	110	122	123	132	133	138	148	158	158	189	204
62	190	199	115	120	128	127	130	132	143	153	158	158	189	218
63	197	199	118	120	130	133	136	140	152	158	158	169	197	228
63	197	116	122	128	130	136	143	143	152	158	169	169	207	232
65	110	120	120	132	138	140	150	153	162	168	169	170	200	230
65	118	120	130	130	132	148	150	153	162	168	170	180	210	240
66	128	127	130	130	140	158	159	163	162	178	189	188	226	253
68	123	127	138	140	153	158	160	166	172	188	196	197	230	262
68	128	133	132	140	153	162	160	170	182	180	196	203	230	260
69	132	139	140	150	160	162	162	173	182	189	200	203	236	270
70	130	139	150	153	160	162	172	183	198	200	208	203	250	286
72	130	143	150	162	169	172	180	183	199	206	208	223	250	296
73	140	157	150	160	169	182	180	197	200	200	219	227	268	302
73	148	153	160	160	170	180	180	202	200	212	229	233	262	300
75	152	160	168	170	180	180	200	208	210	228	232	240	272	310
76	150	160	168	170	180	192	200	208	220	230	232	240	280	320
76	156	164	172	180	189	197	205	213	221	230	238	246	287	328

^a To determine BMI, find the height in the left-hand column; then move across the row to a given weight. The number above the weight column is the BMI for that height and weight.

^a To determine BMI, find the height in the left-hand column; then move across the row to a given weight. The number above the weight column is the BMI for that height and weight.

^b **Weight** calculations: weight (kg)/height (m)² or (weight [lb]/height [in.²]) × 703.

^b **BMI** 30-34.9 defines Class I obesity, BMI 35-39.9 defines Class II obesity, BMI ≥40 defines Class III obesity.

Key: BMI = Body mass index. BMI 30–34.9 defines Class I obesity; BMI 35–39.9 defines Class II obesity; BMI ≥40 defines Class III obesity.

Key: BMI = Body mass index.

Exclusive use of BMI as an indicator of overweight and obesity has limitations in that it does not consider extreme variation in body composition. Very muscular subjects, for example, may be classified by BMI as overweight or obese when, in fact, they are not carrying excessive adipose tissue. Alternatively, some persons with BMI in the desirable range may have less than optimal muscle mass and a high percentage of body fat. Finally, the optimal BMI range for minimizing the risk of obesity-related CVD may differ among ethnic groups and age categories.⁶ A controversial finding is that of the “obesity paradox”: Several epidemiologic studies indicated a survival benefit for being overweight or mildly obese in some cases of CVD; a 2016 meta-analysis, however, does not support this contention.⁷

The importance of the distribution of body fat to risk for obesity-associated disease and death has been described. Central fat around the waist and deep visceral adipose surrounding internal organs are associated with greater health risk than inert subcutaneous adipose in regions such as the buttock or thigh. Fat cells in the viscera of the abdomen are associated with chronic inflammation, which in turn can contribute to chronic diseases such as CVD, type 2 diabetes, and cancer.⁸ A waist circumference greater than 40 inches for men or 35 inches for women has been considered a risk factor for development of type 2 diabetes and CVD; however, the 2013 review from the USDHHS indicated that use of these cutoffs requires further study.¹ In an effort to better identify and address obesity and its related risks, health care providers are encouraged to take measurements of height, weight, and waist circumference; performance of these physical assessment techniques can be realistically accomplished even in a busy clinical setting.

Metabolic syndrome is characterized by the presence of certain metabolic risk factors and has been associated with increased risk of coronary artery disease, other vascular diseases, and type 2 diabetes. Patients with three or more of the following risk factors are said to have metabolic syndrome:

- Waist circumference greater than 40 inches in men or 35 inches in women (numbers may vary among different ethnic groups)
- Serum triglyceride levels of 150 mg/dL or greater
- High-density lipoprotein (HDL) cholesterol level less than 40 mg/dL in men or less than 50 mg/dL in women
- Blood pressure of 130 mm Hg systolic or 85 mm Hg diastolic or higher
- Fasting serum glucose level of 100 mg/dL or greater

Subjects with metabolic syndrome are likely to demonstrate insulin resistance and may benefit more from weight loss to reduce morbidity and mortality than would overweight or obese subjects without the syndrome. In addition, increased muscle mass is associated with improved insulin sensitivity. Therefore, physical activity promoting increased muscle mass may result in improved insulin sensitivity even in the absence of weight loss.

The Endocrine Society has published guidelines for obesity in children and adolescents that are based on Centers for Disease Control and Prevention growth charts.⁹ These guidelines define a BMI “percentile for age” between the 85th and 95th percentiles as *overweight* and the 95th percentile or greater as *obese*.

Pathophysiology of Overweight and Obesity

Weight gain is, to some extent, a reflection of energy intake exceeding energy expenditure. The physiology of energy intake and expenditure is complex, however, and involves numerous body systems, including the hypothalamic–pituitary axis, autonomic nervous system, central nervous system, endocrine system, gastrointestinal (GI) tract, and adipose tissue.

Both genetic and environmental factors are important in the etiology of overweight and obesity, and a complex interplay between these factors is recognized. The rapid increase in obesity over the past few decades argues for a strong environmental role. Increased portion sizes and caloric intakes no doubt contribute to recent trends in obesity rates. Today’s lifestyle and environment are likely modulating genetic expression of obesity in many susceptible persons. For example, studies have shown that higher intakes of sugar-sweetened beverages and fried foods may predispose people with certain genetic traits to risk for developing obesity.^{10,11} However, consumers

should be cautioned about commercial weight management programs offering genetic analysis as part of their packages; these programs may be beneficial, but marketing may overstate the evidence for their proven utility.

Researchers studying obesity have identified several different hormones and proteins potentially involved in energy balance.¹² Studies are ongoing to determine whether excess or deficiency of or resistance to specific substances may be related to weight homeostasis. Compounds of interest include leptin, peptide YY, ghrelin, and glucagon-like peptide 1. An in-depth discussion of this topic, however, is beyond the scope of this chapter.

Environmental factors contributing to recent increases in obesity include decreased physical activity coupled with increased food availability and consumption, especially calorie-dense foods. Guidelines for regular moderate physical activity are met by only a minority of adults and children in the United States.^{13,14} Initiation of even modest amounts of exercise by sedentary persons can have multiple health benefits, including maintenance of current weight instead of continued weight gain.

Significant increases in portion sizes of food and increased sedentary working hours may be environmental factors contributing to increasing rates of obesity. (See [Chapter 23](#) for a discussion of a healthy diet.)

Another factor of interest in the etiology of overweight and obesity is sleep, with respect to both duration and quality. Several mechanisms have been postulated and studied regarding this association.¹⁵ Sleep deprivation has been associated with decreased leptin and increased ghrelin levels in some studies; these hormonal alterations may potentially lead to increased appetite. People who do not sleep well or who sleep for only short periods each night may engage in more sedentary screen-based activities (e.g., television and computer viewing), which may encourage unhealthy snacking.

Still another concept in the etiology of obesity relates to the gut microbiome.¹⁶ Lean and obese subjects have been found to have different proportions of certain bacteria. Furthermore, these proportions have been shown to change with weight loss. These findings may lead to investigation of prebiotics, probiotics, and antibiotics as tools for weight maintenance and weight loss. (See [Chapter 20](#) for a discussion of prebiotics and probiotics.)

Use of some medications can lead to weight gain.¹⁷ As clearly shown by

abundant evidence, a majority of the second-generation antipsychotics contribute to significant weight gain and related metabolic disorders. Older antidepressants (tricyclics and monoamine oxidase inhibitors) may be associated with modest weight gain (10–15 pounds). Although some of the selective serotonin reuptake inhibitors may produce weight loss, this loss usually is short-lived, and weight gain can eventually occur. Other important groups of medications contributing to significant weight gain are hormonal contraceptives, systemic corticosteroids, certain anticonvulsants, certain sulfonylureas, thiazolidinediones, and insulins. The latter three groups are noteworthy because patients with type 2 diabetes for whom these medications are prescribed frequently are already overweight.

Obesity and Chronic Health Problems

Overweight and obesity are associated with myriad chronic health problems.¹ Many of these problems can be ameliorated with even modest weight loss, defined as about 5% of initial body weight.

Obese persons experience more difficulties in performing activities of daily living, such as walking, climbing stairs, or bending and kneeling. Weight loss can result in improved comfort, safety, and mobility during kneeling.

Obesity is closely associated with cerebrovascular disease. Overweight and obesity are associated with both hemorrhagic and ischemic stroke.¹ Fatal and nonfatal stroke risk increases with increasing BMI.¹ Overweight and obesity are linked to increased risk for hypertension, dyslipidemia, coronary artery disease, and arrhythmias.¹⁸ Prevalence of hypertension begins to increase at relatively low levels of overweight. Weight loss in obese subjects is associated with significant reductions in blood pressure.¹

A correlation between increasing BMI and increasing triglyceride and low-density lipoprotein (LDL) cholesterol levels has been recognized and investigated in some detail. Beneficial HDL cholesterol levels tend to be lower in both men and women with higher BMI values. Modest weight loss of 3–8 kg can have beneficial effects on blood lipid levels, although these effects generally are much less robust than those achieved by greater weight loss and particularly statin therapy.¹

The relationship between overweight and obesity and type 2 diabetes is well documented. Visceral adiposity (large waist circumference) has been shown to be a risk factor for development of type 2 diabetes. Patients who initially are insulin-resistant, typically evidenced by high plasma triglycerides and low HDL cholesterol, are most likely to benefit in terms of reduced morbidity and mortality risk after weight loss. Modest weight loss is effective in improving blood glucose control in patients with type 2 diabetes; addition of orlistat, a weight control drug, may accentuate this effect.¹ Modest weight loss also may help prevent development of type 2 diabetes in persons at risk.^{1,19}

A specific challenge in the management of obesity is combating the effects of widespread negative attitudes toward obese people, leading to social stigmatization and discrimination. The recognition of obesity as a disease by the American Medical Association was a step toward addressing such stigmatization and bias within the medical community. Obese persons may demonstrate self-isolation that leads to constraints in their pursuit of beneficial health care. Overweight children may develop psychosocial difficulties including emotional disorders, depression, and self-esteem issues.

Obesity appears to increase the risk for a number of other disorders, including gallbladder disease, nonalcoholic fatty liver disease, osteoarthritis, sleep apnea, asthma, certain types of cancer, and disorders of female reproductive function.¹ Obesity is a risk factor for hyperuricemia and gout.¹ Overweight is believed to contribute to a significant proportion of certain cancers and increased mortality from cancer.¹ Of particular concern are cancers with a hormonal basis, such as cancers of the breast, prostate, or endometrium, as well as cancers of the colon, rectum, and gallbladder. Hypertension and gestational diabetes are more likely in obese women who become pregnant.

Algorithm: Overweight and Obesity

Figure 27–3 Self-care for overweight and obesity. Key: ACC = American College of Cardiology; AHA = American Heart Association; BMI = body mass index; CVD = cardiovascular disease; DS = dietary supplement; HTN = hypertension; PCP = primary care provider; TOS = The Obesity Society.

Management of Overweight and Obesity

Management Goals and General Management Approach

The three major approaches to weight management are adoption of a healthy lifestyle (i.e., diet and exercise habits), pharmacologic therapy (nonprescription and prescription medications, dietary supplements), and bariatric surgery. A combination of these approaches may sometimes be used. Treatment goals of weight loss can be classified into three main categories: (1) improved control of comorbid conditions and chronic diseases associated with overweight and obesity, such as type 2 diabetes and CVD; (2) improvement in psychological health and feelings of well-being; and (3) cosmetic benefit.

For many people, losing weight or maintaining weight loss is a lifelong challenge. Successful weight loss and subsequent weight maintenance require significant behavioral modification. Pharmacologic therapy with nonprescription agents should be only a short-term measure unless overseen by a health care provider. Long-term use of prescription therapies with appropriate medical supervision may be an option for patients with a BMI of 30 or higher or a BMI of 27 or higher with comorbid conditions.¹⁹ Pharmacologic interventions, however, often result in only modest weight loss that is regained after drug discontinuation. Bariatric surgery may be considered for patients with a BMI of 40 or higher or a BMI of 35 or higher with comorbid conditions, including hypertension and hyperlipidemia.¹⁹ In patients with type 2 diabetes, bariatric surgery is sometimes considered with BMI of 30 to 35. Surgery is effective for helping many patients to achieve weight loss, although success following surgery also requires lifestyle changes. The procedures carry their own significant risks. In addition, weight loss devices (hydrogel capsules, aspiration devices, and endoscopic balloon and sleeve devices) are currently available.

Many chronic diseases and conditions respond favorably to weight loss. In many instances, however, weight loss goals set by the patient are unrealistic and based on desired cosmetic rather than health benefits. Weight loss (and maintenance of that loss) of 5%–10% of initial weight can have positive health effects in persons with hypertension and type 2 diabetes. Guidelines prepared

by the American Heart Association/American College of Cardiology/The Obesity Society state that the initial goal of weight loss is to reduce body weight by about 5%–10% over 6 months.¹⁹ If this goal is achieved and further weight loss is indicated, it can be attempted. The first 10% loss carries the greatest health benefits; it also is easiest to attain, because a decreased basal metabolic rate often causes weight loss to plateau after about 6 months. In many patients, it is more important to maintain the 10% weight loss than to pursue further weight loss, and most patients find weight maintenance to be more difficult than initial modest weight loss. An approach often overlooked may be to prevent further weight gain in people who have slowly but steadily gained weight over a period of years. [Figure 27–3](#) is a guide for the health care provider in recommending weight loss measures.

Nonpharmacologic Therapy: Lifestyle Intervention

Dietary modification or restriction is the mainstay of weight loss therapy. Physical activity is less effective in producing weight loss initially but is important in maintaining weight loss and improving overall fitness. The term *lifestyle intervention* describes a strategy of dietary change, physical activity, and behavior therapy.¹ One major key to weight loss and maintenance of that loss is implementing lifestyle interventions that are sustained over a long period of time. Support for and directed access to lifestyle intervention programs should be included in the array of services available from today's health care providers.

Dietary Change

Dietary change is the most commonly used weight loss strategy. Diet strategies include caloric restriction; changes in dietary proportions of fat, protein, and carbohydrate; use of macronutrient substitutes (i.e., sugar and fat substitutes); and changes in timing or frequency of meals. Short-term success for many methods has been documented; however, data on longer-term effectiveness and safety are less encouraging. Weight loss at the end of relatively short-term programs can exceed 10% of initial body weight. However, a strong tendency to regain weight has been well documented. A relatively small portion of participants do maintain weight loss over more extended periods. The National Weight Control Registry tracks persons who have

maintained weight loss of at least 30 pounds for at least 1 year.²⁰ To initially lose weight, subjects in this registry used a variety of methods; about one half were self-directed methods and half were some type of program. Most participants reported maintaining weight loss through a combination of a low-calorie, low-fat diet and exercise.

Even small changes in dietary patterns can have a positive effect. Cutting portion sizes, switching to water or diet soda rather than sugar-sweetened beverages, using smaller plates for meals, and keeping healthy snacks such as fruits and vegetables on hand are useful, sustainable strategies. Trying to eat foods with low energy density (i.e., low calories per weight of food) may be helpful in that these foods tend to promote satiety. Because lifestyle changes need to be made for the long term, patients should be encouraged to make realistic, smaller changes, rather than opting for more radical fad diets that are difficult to adhere to over time. (See [Chapter 23](#) for more details about healthy diets.)

Caloric Restriction

Daily caloric allowances for moderately active persons vary with age, gender, and body weight. Overall, the U.S. population suffers from “portion distortion,” and people need to relearn appropriate food portion sizes based on age and activity levels. Daily caloric intake allowances for a reference 30-year-old man (weight, 154 lb; height, 5 ft 10 in.) in a temperate climate are approximately 2400–3000 kcal/day, depending on activity level. Corresponding figures for a reference 30-year-old woman (weight, 126 lb; height, 5 ft 4 in.) are approximately 1800–2400 kcal/day.²¹ These figures are lower for older adults and higher for younger adults. Caloric requirements for women increase during pregnancy and lactation (see [Chapter 23](#)).²¹ Self-initiated weight loss during pregnancy is not generally recommended.

A diet that is individually planned and designed to create a deficit of 500 kcal/day or more should be an integral part of any weight loss program.¹ A low-calorie diet (LCD) of approximately 1200–1800 kcal/day may involve a structured commercial program, or it may involve guidelines for selecting conventional foods, including careful attention to portion sizes. Initial weight loss with an LCD typically is 1–2 pounds per week. A very-low-calorie diet (VLCD) of 800 or fewer calories per day, as indicated in certain circumstances, should be monitored under medical supervision and accompanied by high-

intensity lifestyle intervention.¹ VLCDs frequently consist of liquid formulas given several times a day. Although weight loss with VLCDs over 12–16 weeks typically is double that with LCDs, long-term results are often no better. A multivitamin and multimineral preparation should be recommended for patients consuming fewer than 1200 kcal/day for prolonged periods.

Another strategy for weight loss and maintenance receiving increasing attention is fasting and time-restricted eating. Various approaches have been described, including eating only within a time frame of 6–10 hours each day, eating regularly for 5 days a week and consuming restricted calories 2 days a week, and alternate-day fasting. Preliminary evidence has given the signal that such approaches may have beneficial effects on weight control and metabolic and cardiovascular risk factors.²² However, further randomized controlled trials with clinical outcomes are needed. These approaches generally have been associated with only minor adverse events so long as the fasting is short term.

Altered Proportions of Food Groups

The 2010 Dietary Guidelines for Americans recommended a diet supplying no more than 35% of total calories from fat, of which no more than 10% of total calories come from saturated fat.²³ The 2015–2020 Dietary Guidelines still recommend a diet low in saturated fat but do not state a ceiling for percentage of overall fat in the diet.²¹ A low-fat diet alone is inadequate for weight loss; the diet must also reduce total calories.

Very-low-fat vegetarian diets in the context of other lifestyle changes have been advocated. Although such programs can result in regression of coronary atherosclerosis and improvement of endothelial function in some patients with moderate to severe coronary heart disease, their applicability to larger populations remains questionable with regard to compliance. Dietary fats must be carefully chosen for a very-low-fat diet to prevent essential fatty acid deficiency. Such diets increase triglyceride levels and lower HDL cholesterol in the short term because of the high carbohydrate content.

A spectrum of popular high-protein, higher-fat, and low-carbohydrate diets have been described. Some contain very low amounts of carbohydrates (supplying approximately 5%–15% of total calories; e.g., the Atkins diet) and are ketogenic, whereas others are considered moderate-carbohydrate diets (supplying approximately 35%–50% of calories from carbohydrate; e.g., the

Zone diet). People often start out on the “ultralow” form of the diet, with subsequent transition to a more moderate form. Part of the success of low-carbohydrate diets may lie in the fact that they simplify food choices, thus facilitating dietary adherence.

Very-low-carbohydrate diets prevent the elevated insulin levels that promote storage of body fat. Much of the weight loss seen with these diets is a result of decreased caloric intake from avoiding high-carbohydrate foods. Initial weight loss results in part from a diuretic effect and glycogen depletion. Low-carbohydrate diets result in significant weight loss over 6–24 months. Long-term effects of these diets on CVD risk are still largely speculative.¹ Low-carbohydrate diets generally have more favorable effects on triglycerides and HDL cholesterol levels, whereas low-fat diets have more favorable effects on LDL and total cholesterol.¹ Some research has indicated that weight loss associated with low-carbohydrate diets is associated with smaller decreases in resting energy expenditure compared with weight loss achieved with low-fat diets; this might help with maintenance of the weight loss.²⁴

Potential adverse effects of low-carbohydrate diets include lack of essential nutrients such as potassium, calcium, and magnesium. High-protein foods consumed in large quantities on these diets could increase uric acid levels and precipitate gout, although this problem has not been common in studies with up to a year of follow-up. High animal protein content promotes calcium excretion in the urine, which could be deleterious to bone health. Restriction of fruits, vegetables, whole grains, and milk products may potentially increase the risk for various cancers by depleting essential vitamins, minerals, and fiber and also lead to constipation. High protein content may predispose the dieter to dehydration and hyperfiltration by the kidneys, leading to eventual kidney damage, particularly in diabetic patients. Headache, muscle weakness, and fatigue are other adverse events reported by some persons on low-carbohydrate diets.

Several published randomized trials of these diets demonstrated relative safety of the low-carbohydrate, higher-fat, high-protein diets for 2–24 months, with greatest weight loss seen in the first 6 months.²⁵ In the Women’s Health Initiative trial, reduction in total fat intake for 8 years did not reduce risk for CVD.²⁶ This finding may be related to the observation that when compared with fat-restricted diets, carbohydrate-restricted diets have more favorable effects, not only on triglyceride and HDL cholesterol levels but also on small

dense LDL cholesterol mass.²⁶

Low-glycemic-index food products are promoted commercially. *Glycemic index* refers to the amount of blood glucose rise seen over a set period of time after ingestion of a standardized amount of a food. Many high-carbohydrate, low-fat diets are associated with a high glycemic index for the foods ingested. Through careful selection of dietary carbohydrates, a lower glycemic response can be obtained. Low-glycemic-index diets could be expected to promote satiety and prevent large fluctuations in insulin concentrations and may help maintain insulin sensitivity. Studies have not consistently supported the usefulness of low-glycemic-index diets in weight control, and the methods used to classify foods with this system are controversial.

Use of Food Additives

Some patients may use food additives such as artificial sweeteners and fat substitutes to reduce caloric intake. Although theoretically the use of these agents should help decrease caloric intake, existing data and recommendations are conflicted regarding the beneficial and detrimental effects of these products. [Table 27–2](#) outlines information related to sugar and fat substitutes.

Table 27–2 Common Sugar and Fat Substitutes	
Substitute (With Selected Trade Name)	Comments
Sugar Substitutes	
Saccharin (Sweet'n Low) ^a	Has bitter taste; has been replaced largely by newer sweeteners
Aspartame (NutraSweet) ^a	Contains phenylalanine, so contraindicated in patients with phenylketonuria; not for use in cooking or baking as heat breaks it down into free amino acids, which impart a bitter taste
Fructose	Nutritive sweetener that should not be viewed as sugar free; insulin not required for fructose utilization in the body; contains approximately 10 calories when supplied in an amount providing the equivalent sweetness of about 1 teaspoon of sucrose

Substitute (With Selected Trade Name)	Comments
Sorbitol	Nutritive sweetener that should not be viewed as sugar free; does not cause tooth decay but can cause osmotic diarrhea when ingested in large quantities; contains approximately 10 calories when supplied in an amount providing the equivalent sweetness of about 1 teaspoon of sucrose
Xylitol	Nutritive sweetener that should not be viewed as sugar free; does not cause tooth decay; contains approximately 10 calories when supplied in an amount providing the equivalent sweetness of about 1 teaspoon of sucrose
Acesulfame potassium (Sweet One) ^a	May be substituted for sucrose in cooking; may be combined with aspartame, because some people detect a metallic aftertaste with acesulfame potassium alone
Sucralose (Splenda) ^a	May be used in cooking
Neotame ^a	Chemically similar to aspartame; may be used in cooking
Cyclamates ^a	Banned by FDA in 1969 because of association with cancer in animals; applicability of this finding to humans has been challenged; remains available in many countries
Advantame ^a	Approved by FDA in United States as of 2014; 20,000 times sweeter than sugar; not commonly used
Stevia (Truvia) ^a	Approved by FDA in United States as of 2008 as a food additive in a specific purified form
Fat Substitutes^b	
Microparticulated protein (Simplese)	Used in frozen desserts, salad dressing; unstable if heated
Soluble fiber (Oatrim)	Derived from oats and designed to replace fat in meats, cheeses, baked goods, and frozen desserts
Sucrose polyester (Olean)	Also known as olestra; is not absorbed; can cause malabsorption of fat-soluble vitamins; possible GI adverse effects with ingestion of large quantities; can be used for cooking and frying

^a Can be labeled as noncaloric based on FDA labeling regulations; cyclamates no

longer approved by FDA for use as sugar substitute.

^b Use of these fat substitutes in food products in place of fat typically decreases caloric content of the foods by about half, unless extra sugars are added to the products.

Key: FDA = U.S. Food and Drug Administration; GI = gastrointestinal.

Meal Replacement Therapy

Diets that use meal replacement foods typically involve replacing up to 2 meals a day with a liquid drink, snack bar, or measured frozen meal, with the dieter encouraged to eat a “reasonable” third meal each day. The main advantage to this approach is portion control. Products typically contain about 200–300 kcal per serving and are low-fat foods, although low-carbohydrate options also are available. The challenge with this approach is that dieters enter their third meal extremely hungry and may consume excessive calories by overeating at this time. Early weight loss with these products, part of which may be a result of low sodium content leading to water loss, can give a psychological boost to adhere to the program. Meal replacement products are discussed further in [Chapter 24](#).

Commercial Weight Loss Programs

Structured commercial weight loss programs such as Weight Watchers, Jenny Craig, and Take Off Pounds Sensibly (TOPS) are very popular in the United States. Women tend to gravitate to these programs more frequently than men do. Participation in structured commercial programs may be expensive if subjects are required to purchase program-specific tools as well as specially packaged snacks or meals. The success seen with these programs is likely at least partially due to the social support that develops with periodic meetings. Online tools such as diet and exercise diaries and support groups are increasingly available; these resources may be less expensive than community-based structured commercial programs.

Physical Activity

Encouragement of physical activity for preventing overweight and obesity is an important public health strategy for all age groups, including children. The

U.S. Department of Health and Human Services outlines the physical activity recommendations shown in [Table 27–3](#).²⁷ For older adults, regular exercise can reduce functional declines that occur with aging.

Table 27–3 Physical Activity Recommendations^a	
Children and Adolescents	
<i>Aerobic:</i>	≥60 minutes of moderate or vigorous aerobic activity a day, including vigorous activity at least 3 days a week
<i>Muscle and bone:</i>	Strengthening physical activity should occur at least 3 times a week
Adults	
<i>Aerobic:</i>	150–300 minutes of moderate aerobic activity or 75–150 minutes of vigorous physical activity a week, performed in ≥10-minute episodes ^b
<i>Muscle:</i>	Strengthening activities involving major muscle groups should occur at least twice a week

^a As proposed by the U.S. Department of Health and Human Services in *Physical Activity Guidelines for Americans, 2018*.²⁷

^b More activity than is outlined here is necessary to promote weight loss in most people. Exercise should be used in combination with dietary restriction to promote weight loss.

Increased physical activity is an important component of weight loss therapy and is even more important in weight maintenance after weight loss. Persons who regularly exercise may, in general, be more committed to a healthy lifestyle. Exercise builds muscle, which has a higher metabolic rate than a corresponding amount of fat. Weight loss that can be achieved by an exercise program is modest; combining a reduced-calorie diet with increased physical activity produces greater weight loss and reduction in abdominal fat than can be achieved with either approach alone. Patients who have restrictions as to types of exercise should have a medical evaluation before starting an exercise regimen. Regardless of presence of concomitant diseases, current recommendations call for men older than age 40 and women older than age 50 to undergo a medical evaluation before starting an exercise program.

For sedentary patients, a walking program often is a good place to begin. A pedometer or other inexpensive activity tracker may be an aid to increasing activity in some persons. Patients can start by walking 30 minutes each day for 3 days a week, building up to at least 60 minutes of moderate-intensity physical activity most days of the week. The 60-minute activity periods can be accrued in multiple smaller increments throughout the day with similar benefit. Patients should be encouraged to participate in activities that they enjoy and are therefore more likely to continue.

Behavioral Therapy

Behavioral therapy used in combination with other strategies, such as diet, exercise, and medications, can improve the outcome of weight loss programs. Behavioral interventions are most effective when patients participate in sessions at least once or twice a month.⁵ Behavioral therapy may be administered in either an individual or a group setting by professionals or lay leaders. Remote coaching and mobile technologies are increasingly being explored as less expensive methods for encouraging adherence to lifestyle modifications. Behavioral techniques include self-monitoring of weight; use of tools such as pedometers and food scales; and problem solving to identify barriers to weight loss and maintenance.⁵

Public Health Initiatives

In an era when federal and state governments bear an increasing percentage of the cost of health care in the United States, interest in public health initiatives to decrease overweight and obesity has increased. Efforts at all levels of government to require dietary information in restaurant menus, to limit portion sizes of sugar-sweetened beverages, to eliminate trans-fat content in commercial foods, and to levy taxes on certain unhealthy foods are just a few examples of initiatives that have been considered or actually implemented. Many schools have banned the sale of sugar-sweetened beverages and high-fat snacks on their premises. These measures are controversial, and positive benefits on public health are not consistently shown at this time.

Pharmacologic Therapy

Pharmacologic therapy is generally not recommended for weight loss. In recent years, many more weight loss products have been removed from the

market for safety reasons than were approved. The ideal weight loss drug, which would provide fast and permanent weight loss with no adverse effects, does not exist despite the billions of research and consumer dollars spent on weight loss products every year.

Guidelines for obesity and overweight management recommend weight loss medications only for adjunct therapy to lifestyle interventions in patients with either a BMI of 30 or greater or a BMI of 27 or greater associated with concomitant diseases or risk factors.¹⁹ Recent guidelines on overweight and obesity treatments did not specifically address medication therapy for weight management because of the scarcity of medications approved for chronic management of obesity. Since publication of updated guidelines, additional medications have been approved for weight loss.¹⁹ These guidelines should apply to all weight loss products (prescription or nonprescription drugs and dietary supplements), although nonprescription orlistat (allī) can be used in patients with a BMI of at least 25, as discussed in the following section. Weight loss medications and supplements should be used in conjunction with lifestyle intervention and should be continually assessed for efficacy, safety, and tolerability.

Status of Nonprescription Weight Loss Products

Since 1991, FDA has banned more than 100 weight control ingredients in nonprescription drug products, including phenylpropanolamine, ephedrine, aloe, and cascara sagrada.²⁸ Ephedrine alkaloids are contained in several botanicals, including sea grape, yellow horse, joint fir, popotillo, ma huang, and country mallow. Although these products are banned from sale in the United States, other substances that may pose similar risks are still included in dietary supplements and often are found as components of weight loss products.

In the period 2013–2015, FDA sent warning letters to several manufacturers of products containing BMPEA (beta-methylphenethylamine), DMBA (1,3-dimethylbutylamine), and DMAA (1,3-dimethylamylamine).^{29–31} FDA does not consider BMPEA, DMBA, and DMAA to meet the legal definition of a dietary ingredient, primarily because these substances are not from botanical sources, regardless of the manufacturers' claims. FDA warns consumers to avoid products containing these ingredients because of potentially dangerous adverse effects, such as hypertension and cardiovascular problems.

Dietary supplements are distinct entities from nonprescription drugs. They include herbal and other products meant to supplement the diet and are regulated under the Dietary Supplement Health and Education Act of 1994 (see [Chapter 50](#)).

A majority of drugs currently considered safe and efficacious for weight loss have prescription-only status and include benzphetamine (Didrex), diethylpropion (Tenuate), methamphetamine (Desoxyn), orlistat (Xenical), phendimetrazine (Bontril), phentermine (Ionamin), phentermine/topiramate (Qsymia), lorcaserin (Belviq), naltrexone/bupropion (Contrave), and liraglutide (Saxenda). Another agent, sibutramine (Meridia), was withdrawn from the U.S. market in 2010. Standard pharmaceutical references can be consulted for more information about these drugs.

Orlistat was approved by FDA as a prescription weight loss medication (Xenical) in 1999 and as a nonprescription weight loss medication (allī) in 2007.³² The prescription strength of orlistat (120 mg) is approved for use in patients ages 12 years and older; however, the nonprescription strength (60 mg) is approved only for patients 18 years and older.

Orlistat aids in weight loss by decreasing absorption of dietary fats. It inhibits gastric and pancreatic lipases and specifically reduces absorption of fat by inhibiting hydrolysis of triglycerides.³³ Orlistat should be used in conjunction with a reduced-calorie, low-fat diet and exercise program. The labeling for the prescription product states that the drug is indicated for obese patients with a BMI of at least 30 or for patients with a BMI of 27 or higher who also have risk factors such as diabetes, hypertension, or dyslipidemia. The labeling for the nonprescription product simply states that the drug is indicated for use in overweight adults, which by the standard definition would be persons with a BMI of 25 or greater.³²

The recommended dosage of prescription-strength orlistat is 120 mg taken 3 times a day before meals containing fat; at this dosage, it inhibits dietary fat absorption by about 30%.³³ The nonprescription form of the drug is recommended at a dosage of 60 mg taken 3 times a day before meals containing fat; its inhibition of fat absorption is approximately 25%.³⁴ With either dosage of orlistat, the risk of greasy diarrhea increases as the amount of fat increases in a meal. Because of its mechanism of action, the drug need not be given with a fat-free meal.

Most studies have used the 120-mg dosage in combination with a reduced-calorie diet and have reported modest weight losses, especially during the first 6 months of therapy. In one study with the 60-mg nonprescription dose, weight loss after 16 weeks in the active drug group was significantly greater than in subjects receiving placebo (3.05 kg versus 1.90 kg; $P < .001$).³⁵ In another study, patients on orlistat 60 mg lost an average of 8.5 kg after 1 year of treatment.³⁶ The nonprescription product labeling notes that most patients lost 5–10 pounds (about 2–5 kg) over 6 months in clinical trials.³⁷ Patients receiving orlistat have had significantly greater reductions in LDL cholesterol and blood pressure compared with placebo.³³ Effects on lipid levels may be independent of weight loss, whereas the changes in blood pressure probably are largely due to weight loss. Orlistat 120 mg has been shown to be effective in preventing and delaying development of type 2 diabetes over a 4-year period in patients with impaired glucose tolerance.³⁸

Although the 120-mg dose of prescription orlistat also is indicated for weight maintenance, nonprescription orlistat is indicated only for weight loss and should be discontinued once the patient's BMI has reached 25 or less.

Nonprescription orlistat may be of benefit as an adjunct to lifestyle changes in helping patients lose a modest amount of weight. Results will be more favorable when use of this agent is combined with a reduced-calorie, low-fat diet and increased physical activity. With appropriate patient education, orlistat has the ability to promote change in eating habits, both to optimize the drug's effect on fat absorption and to minimize its adverse effects. Rather than suppressing the appetite, an effect that goes away once the drug is discontinued, orlistat is of benefit in that the patient knows to choose food with lower fat content. Once orlistat is discontinued, adherence to healthier food choices can be maintained.

Patients should be made aware that the adverse GI effects of the medication are likely to be exacerbated by concomitant ingestion of a low-carbohydrate, high-fat diet. Some concern has been raised that this nonprescription agent may be misused, particularly by adolescents; in clinical practice, it would be prudent to watch for repeated purchases of the preparation by patients in this age group.

Orlistat may decrease absorption of fat-soluble vitamins (A, D, E, and K). It is recommended that patients taking this medication take a multivitamin once daily at bedtime or separated by at least 2 hours from an orlistat dose. Orlistat

is minimally absorbed and therefore exhibits little systemic toxicity. Common GI adverse effects are caused by the increased unmetabolized fat present in the GI tract and include flatulence with oily spotting, loose and frequent stools, fatty stools, and fecal urgency and incontinence. Decreasing the amount of ingested fat can minimize these effects. These adverse effects are expected to be less common with the nonprescription dosage, and they generally subside within a few weeks of initiating therapy.

Drug interactions with orlistat are unlikely because of the drug's limited absorption. [Table 27–4](#) lists potential or documented drug interactions with orlistat. Patients with malabsorption disorders should avoid taking orlistat, and patients with a history of thyroid disease, cholelithiasis, nephrolithiasis, or pancreatitis should consult their primary care provider before taking orlistat. Both the prescription and nonprescription strengths of orlistat contain warnings regarding potential liver injury. These warnings are based on rare cases of severe liver injury with orlistat, including one case associated with the nonprescription strength preparation.

Table 27–4 Potential Drug–Drug Interactions With Orlistat	
Drug	Interaction
Cyclosporine	Reductions in cyclosporine concentration may be seen.
Fat-soluble vitamins	Absorption of these vitamins (A, D, E, K) may be decreased.
Levothyroxine	Levothyroxine concentrations may be decreased, leading to hypothyroidism.
Warfarin	Malabsorption of vitamin K may lead to over anticoagulation.
Amiodarone	Starting oral amiodarone during orlistat therapy may result in decreased concentrations of amiodarone.
Antiepileptic drugs	Orlistat could decrease concentrations of various antiepileptic drugs; thiopental, fosphenytoin, and pentobarbital are exceptions.
Antiretroviral drugs	Orlistat may lower the effectiveness of antiretroviral drugs used to treat HIV, possibly owing to inhibition of absorption.

Source: [Reference 33](#).

Orlistat is contraindicated in pregnancy because weight loss offers little potential benefit to a pregnant woman and may result in fetal harm.³³ (See the Preface for a detailed explanation of the pregnancy data.) It is not known if orlistat is excreted into human milk, so caution should be exercised when orlistat is administered to a nursing mother. The safety and effectiveness of the nonprescription orlistat product have not been established for patients younger than 12 years of age. Clinical studies of orlistat did not include sufficient numbers of patients ages 65 years and older to determine whether they show a different response from that seen in younger patients. No dosage adjustment is recommended in patients with renal or hepatic dysfunction.

Use of Inappropriate Medications for Weight Loss

Persons seeking to lose weight will sometimes turn to inappropriate, potentially dangerous methods to induce loss, such as use of diuretics or laxatives. The risks associated with diuretics and laxatives are discussed in [Chapters 9](#) and [15](#), respectively.

Complementary Therapies

Botanicals and Other Preparations

A summary of botanicals commonly used in weight loss supplements is presented in [Table 27–5](#).^{39–43} [Chapter 51](#) provides an in-depth discussion of the more common dietary supplements. Many of these supplements also contain vitamins and minerals, presumably to ensure adequate intake of these essential nutrients by patients on low-caloric diets. In addition, a majority of these supplements contain multiple ingredients with several purported actions. To further complicate the issue, many of the supplements contain “proprietary blends.” Ingredients of proprietary blends must be listed, but their amounts do not have to be specified. Of note, however, for many of these ingredients, scientific evidence for usefulness in weight loss is lacking. To confuse matters further, many herbal extracts are listed by common or not-so-common names (e.g., bitter orange, Seville orange, and sour orange are all common names for *Citrus aurantium*). Many products do not list the botanical name, making it difficult to determine exactly what the herbal product contains. A majority of these products have not been clearly demonstrated to

be effective or safe, and many have been associated with serious adverse effects. Health care providers are advised to carefully review the labels of all dietary supplement weight loss products to determine the risk for adverse reactions and drug–supplement interactions. Broadly speaking, the ingredients of weight loss supplements can be categorized as outlined in [Tables 27–5](#) and [27–6](#).

Table 27–5 Complementary Therapy Agents Commonly Used for Weight Loss	
Agent	Associated Risks
Stimulants, Energy Boosters, and Thermogenic Aids	
Bitter orange (<i>Citrus aurantium</i>)	Synephrine may cause hypertension, cardiovascular toxicity, myocardial infarction, stroke, and seizure.
Caffeine: cola nut (<i>Cola acuminata</i> , <i>Cola nitida</i>); green tea (<i>Camellia sinensis</i>); guarana (<i>Paullinia cupana</i> , <i>Paullinia sorbilis</i>); maté (<i>Ilex paraguariensis</i>)	Caffeine may cause GI distress, nausea, dehydration, headaches, insomnia, nervousness, anxiety, muscle tension, heart palpitations, hypertension, addiction, decreased appetite, and vertigo; avoid in patients with gastric ulcers.
	Use with caution in patients with renal disease, panic disorder, hyperthyroidism, anxiety, or susceptibility to spasm; use only under medical supervision in patients with peptic ulcers, cardiovascular disease, or blood-clotting abnormalities; discontinue use at least 24 hours before surgery; may alter effects of anticoagulant medications.
Forskolin (<i>Coleus forskohlii</i>)	Forskolin is generally well tolerated.
Fat and Carbohydrate Modulators	
Chromium	Chromium is generally well tolerated at low doses.
	Rhabdomyolysis and renal failure may occur with large doses.
	May cause mood and sleep changes, headaches, and cognitive and perception dysfunction.
Cinnamon (<i>Cinnamomum</i> spp.)	Cinnamon is usually well tolerated.
	Allergic reactions, such as dermatitis and gingivitis, may occur with external application and with use of flavored chewing gums, mints, or toothpastes.

Agent	Associated Risks
Conjugated linoleic acid (CLA)	CLA causes GI upset.
Garcinia or brindleberry (<i>Garcinia cambogia</i>)	Garcinia may cause GI distress; acute liver toxicity has been reported
Green coffee	Green coffee is generally well tolerated. Green coffee extract contains caffeine (see Caffeine, listed above).
Green tea (<i>Camellia sinensis</i>)	See Caffeine, listed above.
Licorice (<i>Glycyrrhiza glabra</i>)	Pseudoaldosteronism, hypertension, and hypokalemia may occur.
Pyruvate	GI upset may occur.
Turmeric or curcumin	Curcumin causes GI upset.
	Increased bleeding risk may occur with high doses of curcumin.
Appetite Suppressants and Satiety Promoters	
Damiana (<i>Turnera diffusa</i>)	Damiana may cause diarrhea, headache, insomnia, and hallucinations.
Glucomannan (<i>Amorphophallus konjac</i>)	GI upset may occur; avoid powder or capsule formulations.
Guar gum (<i>Cyamopsis tetragonolobus</i>)	GI upset may occur.
Hoodia (<i>Hoodia gordonii</i>)	No risks have been reported.
Plantain or psyllium (<i>Plantago lanceolata</i> , <i>Plantago major</i> , <i>Plantago psyllium</i> , <i>Plantago arenaria</i>)	Flatulence, GI distress, nausea, and vomiting may occur; ensure adequate water intake to decrease risk of choking and GI obstruction; plantain may reduce absorption of drugs including lithium and carbamazepine.
Fat Absorption Blockers	
Chitosan	Chitosan is generally well tolerated; may cause GI upset, flatulence, nausea, increased stool bulk, constipation; cross-sensitivity may occur in patients with shellfish allergies.
Green coffee	See comments under Fat and Carbohydrate Modulators, listed above.

Agent	Associated Risks
Raspberry ketones extract (<i>Rubus idaeus</i>)	No reliable information about adverse effects of raspberry extract is available. The active ingredient is structurally similar to synephrine; see Bitter orange, listed above.
Carbohydrate Absorption Blockers	
Ginseng (<i>Panax</i> sp.)	Ginseng may cause nervousness, excitement, inability to concentrate, estrogenic effects, Stevens–Johnson syndrome, allergy, and hypoglycemic effects; may interact with several drugs including warfarin, digoxin, and alcohol.
Laxatives and Diuretics	
Cascara sagrada (<i>Rhamnus purshiana</i>)	Abdominal pain, cramps, and diarrhea may occur; chronic use can lead to potassium depletion, disturbed heart function, and muscle weakness; avoid in patients taking digoxin or potassium-depleting diuretics.
Dandelion (<i>Taraxacum officinale</i>)	Avoid use in patients with allergies to ragweed or marigolds (or other members of the Asteraceae/Compositae family); contraindicated in patients with gallbladder or bile duct obstruction, or with bowel obstruction.
Miscellaneous	
Calcium	Constipation, nausea, and vomiting may occur; possibly effective when ingested as naturally occurring calcium in foods, but not when used as a dietary supplement.
Guggul (<i>Commiphora mukul</i>)	GI distress, diarrhea, nausea, and skin rash may occur; use only under medical supervision in patients with hyperthyroidism; may alter effects of thyroid medications, cholesterol-lowering medications, anticoagulants, antiplatelet medications, propranolol, and diltiazem.
Willow bark (<i>Salix alba</i>)	Willow bark is a salicin source; may cause GI upset; avoid in kidney disease owing to potential for reduction in renal blood flow.

Key: GI = Gastrointestinal.

Source: [References 39–42](#). (See also [Chapter 51](#) for additional related information.)

Table 27–6 Categories of Ingredients in Weight Loss Dietary Supplements

Category	Purported Mechanism(s)	Selected Ingredient(s)
Stimulants/energy boosters/ thermogenic aids	Increase basal metabolism, increase energy, counteract fatigue	Caffeine, bitter orange
Fat and carbohydrate modulators	Alter fat or carbohydrate metabolism, resulting in decreased body fat mass and increased lean muscle mass	Green tea, chromium, garcinia
Appetite suppressants and satiety promoters	Reduce caloric intake by suppressing appetite or promoting satiety	Guar gum, glucomannan, psyllium
Fat absorption blockers	Block intestinal absorption of dietary fat	Chitosan
Carbohydrate absorption blockers	Block intestinal absorption of dietary carbohydrate	Kidney bean extract, mung bean extract
Cortisol blockers	Block stress-induced release of cortisol to avoid cortisol-induced increased appetite and fat storage	Beta-sitosterol, phosphatidylserine, theanine
Laxatives	Promote weight loss by increasing fecal loss	Cascara sagrada, psyllium
Diuretics	Promote weight loss by increasing urination and fluid loss	Dandelion, caffeine

Herbal laxatives and diuretics often are included in multiple-ingredient dietary supplements marketed for weight loss. For example, so-called dieter's or "slimming" teas contain a variety of botanical laxatives and diuretics. Diuretics, whether herbal or drug, may result in an initial transient weight loss, but this effect lasts only a few days. Herbal or drug laxatives typically act in the colon and will therefore not decrease caloric absorption in the small intestine, which is the primary site of food absorption. Many of these botanicals are stimulant laxatives that should be used for only 1–2 weeks at a time. Prolonged use may lead to electrolyte imbalances and dependence on the laxative for regular

bowel movements (*cathartic colon*), as discussed in [Chapter 15](#).

Herbal sources of caffeine often have been used in combination with ephedra and willow bark (a source of salicin) for weight loss because of purported synergistic effects. This combination is often referred to as a “fat-burning stack” or ECA (ephedrine-caffeine-aspirin), with claims of additive thermogenic or heat-producing effects.^{42,43} However, adverse reactions to these products, either alone or in combination, have been reported, ranging from relatively mild symptoms, such as headache, nervousness, or hypertension, to more severe afflictions including stroke, myocardial infarction, and sudden death. In several cases, significant adverse events occurred in otherwise healthy young or middle-aged adults, and many such events followed consumption of relatively low doses for short periods.^{42,43}

Since FDA banned ephedra-containing dietary supplements in 2004, many weight loss medications now contain bitter orange (*Citrus aurantium*), often in combination with sources of caffeine such as cola nut (*Cola acuminata* or *Cola nitida*), guarana (*Paullinia cupana* or *Paulinia sorbilis*), or maté (*Ilex paraguariensis*). Bitter orange contains synephrine, which is structurally similar to epinephrine, and octopamine, which is similar to norepinephrine. Bitter orange is touted as a safe alternative to ephedra in many herbal weight loss products. Although adrenergic effects of synephrine and octopamine may suppress appetite and increase lipolysis, these products have the same potential health risks as for ephedra. In a study of healthy adults, a single dose of *C. aurantium* increased heart rate and blood pressure significantly compared with placebo. However, those effects may have been due to the combination of *C. aurantium* with caffeine and other stimulants in the multicomponent product used in the study.⁴⁴ Clinical trials of *C. aurantium* for weight loss have failed to support efficacy for this indication.

Economically Motivated Adulteration

Although adulteration of medications is not a new concept, it is of increasing concern in the dietary supplement industry. A working definition of *economically motivated adulteration* proposed by FDA is the “fraudulent, intentional substitution or addition of a substance in a product for the purpose of increasing the apparent value of the product or reducing the cost of its production, i.e., for economic gain.”⁴⁵ FDA tracks tainted supplements; the most common issue related to weight loss supplements is the undisclosed

inclusion of sibutramine, a prescription weight loss medication that was voluntarily withdrawn from U.S. and Canadian markets because of an associated increased risk of heart attack and stroke in patients with concomitant CVD.⁴⁶ Such adulteration, whether intentional or unintentional, is of particular concern in the weight loss dietary supplement industry, because increasing numbers of cases characterized by the potential for serious adverse events are appearing in the literature.

Assessment of Overweight and Obesity: A Case-Based Approach

Before recommending a weight loss method or product, the health care provider should first determine the patient's motivation for weight loss. The reason may be immediately obvious with some patients; others may want to lose a few pounds to improve their appearance or to enhance their perception of good health (or to comply with medical recommendations for management of a chronic condition). The initial assessment should include measurement of the patient's waist circumference and calculation of the patient's BMI. A careful review of the patient's current medication history (prescription and nonprescription), including use of herbal products and other dietary supplements, is essential. A family history of overweight and obesity is important to recognize, and eating habits (e.g., food types, number and timing of meals) should be identified.

The assessment also should ascertain what weight loss strategies were used previously and whether the attempts were successful. Such strategies may include dietary counseling or physical activity training the patient may have received in the past or is currently receiving. The patient's support system should be considered; support from family and friends is a critical component for success. Similarly, cultural background should be considered because cultural and social factors have a strong effect on food decisions. Such factors should not be seen as insurmountable obstacles. The health care provider can serve an important role to motivate and encourage the patient in weight loss.

Using all information obtained during the assessment, the health care provider can determine whether weight loss is indicated and, if so, can help select a weight loss program of appropriate type, intensity, and duration. Patients with

significant comorbid conditions in addition to obesity should be discouraged from using dietary supplements. For persons within the normal height and weight range who want to lose weight for other reasons (e.g., improved appearance, enhanced sense of well-being), the difficulties involved and the potential for adverse physical and psychological effects with certain interventions should be underscored; often the focus on diet to achieve reduction in body weight can be redirected to a commitment to healthy exercise to attain the desired results.

Cases 27–1 and 27–2 illustrate assessment of two different patients who seek assistance with weight control.

Case 27–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient has been overweight since the age of about 30 years. He was a jockey in his teens and 20s, so he had to restrict his eating to keep his body weight below specified limits. After "retiring" from racing, however, he gained weight.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Patient is a rancher and eats when stressed, particularly at harvest and calving time.
c. Description of the patient's efforts to relieve the symptoms	Patient has not really tried formal diet programs. He is very active in his vocation, but this has not prevented him from gaining weight.
d. Patient's identity	Don Smart
e. Patient's age, gender, height, and weight	42 years, male, 5 ft 4 in., 170 lb

f. Patient's occupation	Rancher
g. Patient's dietary habits	Usually eats eggs, bacon, and toast for breakfast. Usually eats a couple of roast beef or ham sandwiches for lunch. Dinner typically consists of a steak, potatoes, bread, and dessert eaten while watching television with his wife. He drinks a lot of sweetened tea and soft drinks during the day. He also consumes, on average, 2 to 3 beers each evening.
h. Patient's sleep habits	Goes to bed late and gets up early; averages about 6 hours of sleep per night throughout the week.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Takes lisinopril for hypertension, which is currently well controlled. Takes aspirin or ibuprofen occasionally for aches and pains, and lansoprazole as needed for heartburn.
j. Food/drug allergies	NKA
k. History of other adverse reactions to medications	None
l. Other (describe) _____	
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Mr. Smart's BMI is 29, placing him in the overweight category (Table 27-1). Poor dietary habits and inadequate sleep probably contribute.
3. Identify exclusions for self-treatment (Figure 27-3).	None identified.
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer Mr. Smart to a dietitian for dietary advice. (2) Refer Mr. Smart to reputable websites such as myfitnesspal.com for tracking food intake. (3) Refer Mr. Smart to a support group such as Weight Watchers.

	(4) Counsel on diet. (5) Recommend a dietary supplement for weight loss. (6) Recommend orlistat. (7) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Mr. Smart chooses to try to get his wife, who also is overweight, on board for them to lose weight together. She is the primary cook, so she will need advice on healthy, lower calorie meal preparation. Mr. Smart also agrees to switch to water as his primary beverage throughout the day, and to cut back on his beer consumption.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Cut back on calorically dense beverages. Reduce portion sizes. Eat mindfully; eating dinner while watching television may contribute to overeating."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Your exercise level is adequate. Your emphasis should be on making healthy diet choices that are enjoyable to you and to establish eating habits that are sustainable."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
a. Appropriate dose and frequency of administration	n/a
b. Maximum number of days the therapy should be employed	n/a

c. Product administration procedures	n/a
d. Expected time to onset of relief	n/a
e. Degree of relief that can be reasonably expected	“Loss of 1–2 pounds per week is a robust goal of dieting. Loss of even 10 pounds can be beneficial for lowering blood pressure. Maintenance of weight loss can be difficult but is important.”
f. Most common adverse effects	“The more weight you lose, the harder it becomes to lose more weight, because your energy expenditure level drops. Try not to become discouraged when you reach a plateau of weight loss.”
g. Adverse effects that warrant medical intervention should they occur	Criterion does not apply in this case.
h. Patient options in the event that condition worsens or persists	“Consult a dietitian for diet advice. The nonprescription drug orlistat may be an option to help lose weight, although it can have adverse gastrointestinal effects in persons consuming high-fat diets such as yours.”
i. Product storage requirements	None
j. Specific nondrug requirements	“Dietary caloric restriction and exercise are of greatest importance in losing weight. Attempt to reduce stress and thus stress eating. Keep healthy snacks such as fruits and vegetables close at hand during the day. Too little sleep has been associated with increased body weight, so sleep hygiene measures may be helpful.” (See Chapter 46 .)
Solicit follow-up questions from the patient or caregiver.	“Are nuts a good thing for me to snack on?”
Answer the patient’s or caregiver’s questions.	“Nuts are an excellent source of many micronutrients and healthy fats. They do tend to be calorically dense, so portion sizes should be controlled.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Ask Mr. Smart to weigh himself twice a week and to record these values. He should return to you in a month

to report on his progress and to discuss his diet. A weight loss of a few pounds over the first month should be considered a success.

Key: BMI = Body mass index; n/a = not applicable; NKA = no known allergies.

Case 27-2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	An adolescent girl accompanied by her mother is concerned about her weight. She has been considered overweight since preschool. She would like to lose weight to avoid being teased at school.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Patient spends most of her day reading and watching television. She has a limited diet consisting mostly of pizza, macaroni and cheese, hot dogs, potato chips, and sweets.
c. Description of the patient's efforts to relieve the symptoms	The patient has tried eating less but has not formally tried to diet since her parents think her weight is normal and healthy.
d. Patient's identity	Taylor Wolfe
e. Patient's age, gender, height, and weight	12 years, female, 4 ft 10 in., 110 lb
f. Patient's occupation	Seventh-grade student

g. Patient's dietary habits	She eats cereal and 2% milk for breakfast with orange juice. She eats lunch in the cafeteria at school. She has a snack after school, usually potato chips or cookies. She eats dinner, including dessert, with her family every night.
h. Patient's sleep habits	Averages about 9 hours of sleep a night.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	None
j. Food/drug allergies	NKA
k. History of other adverse reactions to medications	None
l. Other (describe) _____	Patient participates in physical education classes at school every day. She has no other regular exercise activity. Both parents and her older sister and brother are overweight.
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Taylor's BMI is 23, placing her in the 90th BMI percentile for age and thus in the overweight category. Her current weight status is associated with increased risk for type 2 diabetes, high cholesterol, hypertension, sleep apnea, and orthopedic problems during adolescence and adulthood. Regular consumption of high-fat and salty snacks and lack of adequate physical activity are contributing to her weight problem.
3. Identify exclusions for self-treatment (Figure 27-3).	Age younger than 18 years is an exclusion for self-treatment.
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer Taylor to a health care provider for a health screen. (2) Refer Taylor to a dietitian and a personal trainer for diet and exercise advice, respectively. (3) Recommend a dietary supplement weight loss product.

	(4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Refer Taylor to a health care provider for a health screen.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Your health care provider may refer you to a dietitian and/or a personal trainer, or the provider could also offer prescription-strength orlistat."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"You need to see your health care provider to determine whether a diet and exercise program is appropriate. Healthy eating habits and exercise are the mainstays of successful weight loss, and these should be a lifelong goal."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	Criterion does not apply in this case.
Solicit follow-up questions from the patient or caregiver.	"Is there a nonprescription medication that might work?"
Answer the patient's or caregiver's questions.	"No nonprescription medications are approved or appropriate to recommend in a patient younger than age 18 without referral from a primary care provider."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Taylor's parents within the next week to ensure she has an appointment for further medical evaluation.

Key: BMI = Body mass index; NKA = no known allergies.

Patient Counseling for Overweight and Obesity

The main objective in counseling patients who want to lose weight is to foster realistic goals for weight loss while also promoting a healthy restricted-calorie diet and increased physical activity. The ultimate goal for the patient is to achieve a healthy weight and maintain that weight over the long term. For patients unable to lose weight, the objective is to prevent further weight gain. The box “Patient Education for Overweight and Obesity” lists specific information to provide in patient counseling.

Evaluation of Patient Outcomes for Overweight and Obesity

Successful weight loss generally requires a lifelong commitment to an approach that combines healthy eating and exercise patterns. Realistic weight loss expectations might be loss of 5%–10% of the initial weight over 6 months, or 1–2 pounds per week. The patient should be counseled that weight management is a lifelong process and that regain after loss is typical if good lifestyle habits are not continued. During any weight loss program, the patient should be monitored for healthy eating and exercise patterns; at a minimum, blood pressure should be routinely measured. More extensive physical examination and laboratory measures may be indicated, particularly in patients with comorbid conditions such as hypertension or type 2 diabetes. Follow-up with patients attempting weight loss should be encouraged, preferably monthly or more frequently. In addition to measuring weight at follow-up visits, the health care provider should explore eating habits and exercise patterns with the patient, especially if weight loss is not being achieved. Also indicated is reexamination of the previously determined goals,

along with follow-up on the patient's progress; new goals can be selected or modifications introduced, as appropriate. Referral to a dietitian or personal trainer may be helpful. After the desired weight loss has been achieved, the importance of maintaining healthful dietary and exercise habits should be emphasized in the subsequent evaluation. Referral for pharmacologic therapy or consideration of bariatric surgery may be an option for patients with more significant obesity who fail to lose weight through lifestyle interventions.

Patient Education for Overweight and Obesity

The objectives of self-treatment are (1) to foster realistic weight loss and exercise goals, (2) to maintain a healthy weight, and (3) to prevent further weight gain. Carefully following the self-care measures listed here, together with continued adherence to a safe and effective weight loss program, will help ensure optimal therapeutic outcomes.

Objectives of Self-Treatment:

Prevention of Health Risks of Obesity

- Health risks related to overweight and obesity include the following:
 - Coronary heart disease
 - Type 2 diabetes
 - Sleep apnea
 - Elevated serum triglycerides and dyslipidemia
 - Hypertension
 - Stroke
 - Gallbladder disease
 - Osteoarthritis
 - Certain types of cancers

Nondrug Treatment Guidelines

- Focus on small, gradual changes in eating and exercise patterns.
- Maintain realistic goals for weight loss and increased activity levels.
- Eat a low-calorie balanced diet.

- Eat meals at the table, and do nothing else while eating (e.g., no television, texting, or social media interactions).
- Set a regular eating schedule, and avoid skipping meals.
- Eat slowly and enjoy the food.
- Put down your fork or spoon between bites.
- Try to leave some food on your plate each time you eat.
- Wait 5 minutes before going back for extra helpings of food.
- Remove serving dishes from the table after the first servings have been made.
- Leave the table, or at least clear food from the table after eating.
- Use smaller plates so that moderate servings do not appear too small.
- Start a meal with a broth-based soup (low salt) to help you feel fuller.
- Strive to consume at least 5 servings a day of fruits and vegetables.
- Keep on hand healthful snacks such as fruits and vegetables, low-fat cheese and yogurt, and frozen fruit juice bars.
- Drink at least 8 glasses of noncaloric beverages each day to help you feel full.
- When you experience a craving, try doing something else, such as going for a walk; cravings generally pass within minutes.
- Avoid eating after dinner.
- Shop for food immediately after a meal, and use a prepared list.
- Gradually increase your activity level, with the goal of engaging in 60 minutes of moderate-intensity physical activity most days of the week.
- Increase your lifestyle activity: Walk and stand more, climb stairs, and park farther from your destination.
- Limit the amount of time spent watching television, playing video games, or using the Internet.
- Keep a diary of your weight, physical activity, and caloric intake so that you can see your progress and success.

Drug Management Guidelines

- Avoid taking nonprescription drugs and supplements marketed for weight loss, with the exception of orlistat. They are not proved to

work, and they can cause significant adverse effects.

- If you do decide to take one of these products, make sure to notify your primary care provider and pharmacist so that you can be adequately monitored for potential adverse effects and drug interactions.
- Both prescription and nonprescription formulations of orlistat are available; be sure you do not take both forms concurrently.

Key Points for Overweight and Obesity

- A reasonable goal for weight loss in most overweight and obese subjects is a 5%–10% loss over 6 months.
- Although this amount of weight loss may not result in the cosmetic effect desired by the dieter, it is associated with a reduction in risk for chronic disease.
- The safest approach to losing weight entails combining a reduced-calorie diet with increased physical activity.
- Physical activity typically needs to be something the dieter enjoys if it is to be sustained over time.
- A key to sustained weight loss is modification of behavior related to eating and exercise.
- If nonprescription or dietary supplement products for weight loss are used, ongoing assessment for efficacy, safety, and tolerance is warranted. It is essential for patients to report all such products used to the health care provider. Labels of nonprescription or dietary supplement weight loss products should be carefully reviewed to determine the risk for adverse reactions and drug–supplement interactions.

Chapter 28: Ophthalmic Disorders

Authors: Richard Fiscella, Michael K. Jensen

The nonprescription ophthalmic products market offers preparations that treat a wide range of eye-related disorders. Limited population-based data are available on the epidemiology of such disorders. People with ocular complaints commonly are first seen in clinical settings including primary care provider practices, hospital emergency departments, and ophthalmologist or optometrist (i.e., eye care specialist) offices; often, however, they initially consult a pharmacist for specific management recommendations.

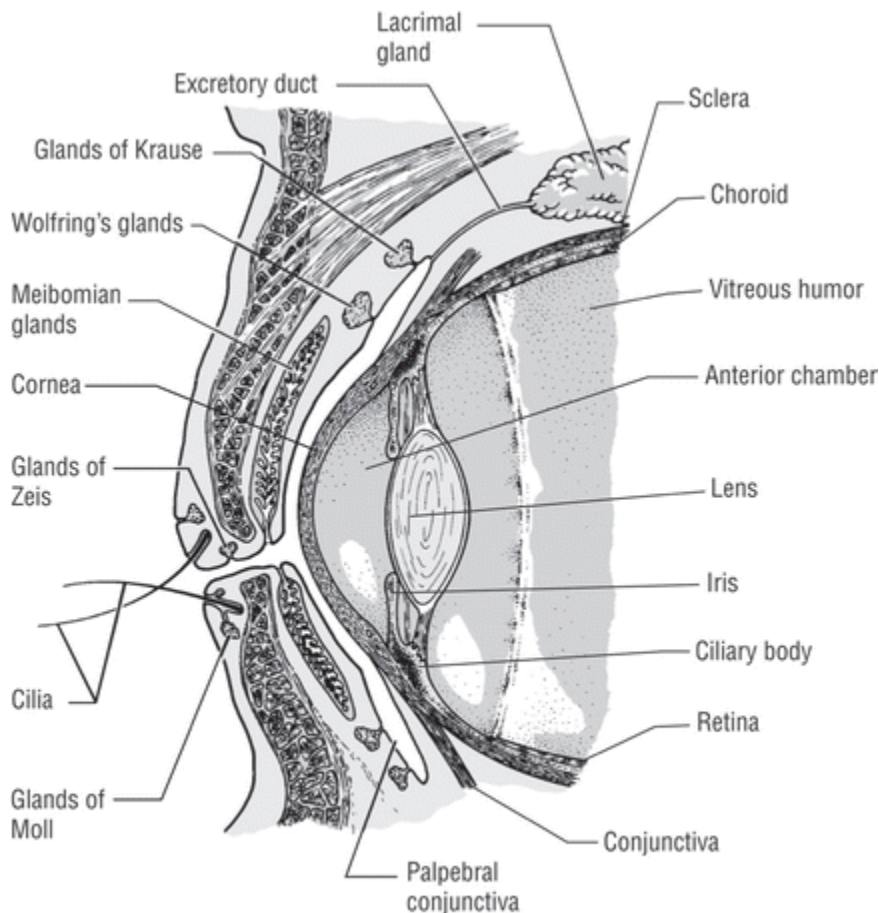
Ocular discomfort associated with dry eye disease may be the most common condition for which use of nonprescription ophthalmic products is appropriate. In the United States, dry eye disease may affect as many as 5 million people 50 years of age and older.¹⁻⁵

Many common conditions that cause ocular discomfort are minor and self-limiting. In some instances, however, relatively mild symptoms may be associated with severe, potentially vision-threatening conditions. Health care providers, including today's pharmacists, should be well versed in eye anatomy and physiology, as well as in common ocular conditions and disorders. This knowledge will enable them to offer the best possible guidance for patients who seek help in choosing between self-treatment and professional medical care.

Self-treatable ophthalmic disorders primarily are those affecting the eyelids; a few disorders and conditions involving the eye surface, however, also may be responsive to self-treatment. The latter group includes dry eye, pinguecula, pterygium, allergic conjunctivitis, corneal edema of known etiology, presence of loose foreign debris, minor ocular irritation, and use of an artificial eye requiring cleaning and lubricating. *Careful assessment is important*, especially with evolving or persistent symptoms, to rule out more complicated disorders or conditions that may necessitate referral to an eye care specialist.

Role of Eye Anatomy in Ocular Drug Pharmacokinetics

The external location of the eye, with concomitant exposure of vulnerable tissues, makes it susceptible to environmental and microbiologic contamination. The eye has many natural defense mechanisms to protect it against contamination, however, and the eyelid is one of its major protective elements (Figure 28–1).



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Figure 28–1 Anatomy of the eyelid and eye surface.

The *eyelid* consists of a multilayer tissue comprising an external skin covering and an internal thin, mucocutaneous epithelial layer called the palpebral conjunctiva. The eyelids also contain the meibomian and smaller accessory glands. The middle layer of the eyelid contains glandular tissue and muscles for lid movement. This specialized glandular tissue, along with conjunctival goblet cells, secretes the bulk of nonstimulated tears.

The eyelids primarily protect the anterior surface of the eye and, through the blink reflex, spread the tears produced by the glandular tissue over the ocular

surface. The lids force the flow of tears toward the nose and into the drainage canals located in the upper and lower eyelids that form what is known as the puncta. The drainage canals converge, forming the lacrimal sac between the inner eyelid and the nose. The lacrimal sac is drained by a canal opening just below the inferior turbinate of the nasal cavity. A highly vascularized epithelium lines the lacrimal drainage system, and absorption into the systemic circulation along this pathway is the means by which topically administered eye medications can produce systemic effects.^{2,3,6}

The *tear layer* keeps the ocular surface lubricated, provides a mechanism for removing debris that touches the ocular surface, and has potent antimicrobial activity conferred by specific enzymes and a number of immunoglobulin proteins (including the most prevalent, immunoglobulin A). The tear layer is a complex, multilayer film. The outermost, lipid layer, which is secreted from the meibomian and accessory glands (i.e., glands of Moll and Zeis) in the eyelid, maintains the optical properties of the eye and reduces evaporation. The middle, aqueous layer is largely responsible for the wetting properties of the tear film. The innermost, mucinous layer allows the lipid and aqueous layers to maintain constant adhesion across the cornea and conjunctiva. Abnormalities within any one of the tear layers can result in ocular discomfort. Commercial artificial tear products often are formulated to mimic the properties of natural tears, to provide effects that are as physiologic as possible.⁷⁻¹⁸

Tears are produced at a rate of 1–2 μL /minute, with a turnover of approximately 16% of the total volume each minute.^{2,3} As much as 25% of the total tear volume is lost to evaporation.^{2,3} An ambient tear volume of approximately 7–10 μL is found on the ocular surface at any given moment.^{2,3} During episodes of ocular irritation, reflex tearing is stimulated by the lacrimal gland found underneath the outer portion of the upper eyelid, and tear production increases to greater than 300% of the non-stimulated production rate.^{2,3} Reflex tearing occurs immediately on instillation of a drug into the eye, diluting the drug's concentration. Drug penetration into the eye is reduced because of this increase in tear production and lacrimal drainage, sufficient to release teardrops that fall down the cheek. Studies have shown that as much as 90% of an instilled dose of a drug administered to the eye may be lost.^{2,3,6}

The visible external portion of the eye is composed of the normally white, noninnervated sclera, and the normally clear, innervated cornea. The *sclera* is a tough, collagenous layer that gives the eye rigidity and encases the internal

eye structures. The visible sclera is covered by two epithelial layers: the episclera and the bulbar conjunctiva. The bulbar conjunctiva is contiguous with the palpebral conjunctiva at the junction between the eyelid and the ocular surface (the fornix). The episcleral and bulbar conjunctival layers (which contain the vascular and lymphatic systems of the anterior eye surface) are the affected tissues in eye redness from ocular irritation or inflammation.

The *cornea* is dome shaped in contour and consists of an avascular tissue that is the principal refractive element of the eye. The cornea is approximately 12 mm wide and 0.5 mm thick and comprises five distinct layers. The pharmacokinetics of ocularly administered drugs is mediated by three of these layers: the outermost epithelium layer, the middle and most abundant stromal layer, and the innermost endothelial layer. The corneal epithelium is lipophilic and facilitates the passage of fat-soluble drugs. However, if a drug is too lipophilic, it may become entrapped in the corneal epithelium. This epithelial sequestering often is the rate-limiting step in absorption of medication into the anterior chamber. The corneal stroma is hydrophilic and allows the passage of water-soluble drugs. Although the single corneal endothelium layer also is lipophilic, it is not considered a barrier to drug penetration.¹⁸

Damage to the corneal epithelium may often increase drug absorption rates. Comparative studies with intact and compromised epithelium have shown that drug penetration into the aqueous humor may be increased as much as threefold in corneas with compromised epithelium.⁷ Corneal epithelium can be compromised by trauma, routine contact lens wear, topical ocular anesthetics, preservatives, or thermal or ultraviolet (UV) light exposure. Compromise of any layer of the cornea can result in significant vision loss and/or scarring.

Directly behind the cornea is the *anterior chamber*, a cavity filled with aqueous humor. The aqueous humor maintains the normal intraocular pressure (IOP) and provides nutritional support for the cornea and crystalline lens. The aqueous humor is produced by the ciliary body and is drained from the anterior chamber through the uveoscleral tract and the trabecular meshwork. The *trabecular meshwork*, which is located at the junction of the cornea and iris, accounts for approximately 80%–90% of aqueous drainage from the anterior chamber. The *uveoscleral tract* (located posterior to the iris and comprising the sclera, ciliary body, and choroid areas) accounts for approximately 10%–20% of aqueous drainage, although this percentage may

vary with age and disease state.

During episodes of internal eye inflammation, inflammatory cells may block the drainage system, causing the IOP to rise. Increased IOP is one of the most significant risk factors for all types of glaucoma, including primary open-angle glaucoma, primary angle-closure glaucoma, secondary glaucoma, and developmental glaucoma. Similarly, during episodes of primary angle-closure glaucoma, the iris physically blocks the trabecular meshwork, which also results in an increase in IOP. Dilating the pupil with mydriatic drugs may precipitate an acute angle-closure attack. These attacks often occur as the pupil is returning to its normal state several hours after the mydriatic drug has been instilled. Any agent with anticholinergic or dilating effects has the potential to cause angle closure. The most common manifestations of this pathologic event are blurred or hazy vision with perception of halos around lights, brow ache, and headache, often accompanied by nausea and vomiting. These symptoms typically are severe enough to cause affected persons to visit an eye care provider.

The visible, colored portion of the eye, the *iris*, is located in the anterior segment of the eye, behind the cornea. It functions in much the same way as for an aperture on a camera by regulating the amount of light striking the retina. The central opening in the iris is the *pupil*. The pupillary diameter is controlled by two opposing muscles within the iris: the sphincter and the dilator. The sphincter muscle runs along circular arcs parallel to the pupillary border and exerts a miotic (closing) effect through parasympathetic stimulation. The dilator muscles are radial from the pupillary border and exert a mydriatic (opening) effect through sympathetic stimulation. Prostaglandins released by the iris during episodes of inflammation may affect the sphincter muscle, resulting in constriction of the pupil.

The *ciliary body* is bordered anteriorly by the iris and is continuous posteriorly with the choroid. In addition to producing aqueous humor, the ciliary body participates in focusing the optical apparatus (lens) for near viewing—a process known as accommodation. During episodes of ocular inflammation, the ciliary muscle may go into spasm, resulting in fluctuating vision and pain. Therefore, inhibition of the ciliary muscle (cycloplegia) with anticholinergic agents is a frequently used approach to treatment of internal ocular inflammation.

The *vitreous cavity*, located in the posterior segment of the eye, is the largest

portion of the eye and is filled with vitreous humor. Floating spots in the visual field, or “floaters,” have their origin here. Floaters are deposits of various shapes, sizes, and motility in the vitreous humor; they may be related to degenerative changes in gel that is normally transparent. Problems in this area are not amenable to self-treatment and require medical evaluation because of the possibility of concurrent retinal problems.

The *retina* is responsible for the initial processing and transmission of light signals. The optic disc, where the optic nerve (cranial nerve II) exits the eye, transmits visual information from the retina to the brain. The macula is an oval-shaped pigmented area near the center of the retina and is responsible for optimal visual acuity. Several inflammatory conditions of the retina can occur, and most are associated with prominent symptoms. Some, however, cause relatively mild symptoms, mimicking common irritative conditions. Trauma, even minor, may cause the retina to separate from its underlying layer (the pigment epithelium)—that is, retinal detachment. The retinal pigment epithelium provides vital “electrical” support to the retina. Macular degeneration, the leading cause of blindness in the United States, is directly related to atrophy in the pigment epithelium and choroidal neovascularization. Diabetic retinopathy and diabetic macular edema also are major causes of vision loss. Potential manifestations of retinal disease that warrant immediate referral to an eye care specialist include subjective perceptions described as “flickering lights” or “a black curtain coming down” and presence of new large or multiple floaters, as well as sudden loss of vision,

Considerations With Use of Topical Ophthalmic Products

Beyond the specific effects of topical ophthalmic products, other factors to consider in the use of these agents include pH, sterility, stability, and expiration date.¹⁸ The pH of the tear film is approximately 7.4 (i.e., physiologically neutral). Of note, however, topical products such as eye drops may be formulated with a lower or a higher pH because of stability and solubility issues. Fortunately, the eye can respond immediately through reflex tearing to help neutralize any pH deviation. A low concentration of buffer in the drug vehicle also has been used to allow the eye’s natural buffering system to reestablish a normal tear pH.

Pharmacologic agents given topically or systemically can affect uptake of topical ophthalmic agents because of their effects on tissue permeability, fluid secretion, and blood flow. Preservatives, buffers, and vehicles may have some effects on drug absorption (see the section “Pharmacologic Therapy” under “Dry Eye Disease”). Systemic agents such as antihistamines may decrease tear film production, thereby also affecting absorption of topical ophthalmic products.

Sterile products are required for topical ophthalmic formulations to be used in the eyes, whether manufactured or compounded. The determination of drug stability is of importance for commercial ophthalmic products.¹⁸ The U.S. Food and Drug Administration (FDA) requires the manufacturer to demonstrate that at least 90% of the labeled concentration of a drug is present in the active form after storage at room temperature for the specified shelf life. A shelf life of more than 18 months usually is recommended for practical considerations, including warehousing and drug distribution, unless consumer demand for the product is high and rapid turnover can be expected. Once a sealed bottle is opened, the contents are subject to the risk of microbial contamination or oxidation from light exposure. Preservatives (see the section “Pharmacologic Therapy” under “Dry Eye Disease”) are essential in multidose topical products to prevent contamination. Some new ophthalmic medication bottles have filtration systems that may allow the contents of the bottle to be preservative free.

The combination of active drug, vehicle, and preservative may result in a hypotonic formulation (<290 mOsm). Buffering agents, salts, and certain sugars often are added to adjust osmolarity of the solution. The tear film has a wide tolerance to osmotic pressure variation. Of interest, hypotonic solutions may be used to relieve dry eye symptoms by helping reduce high tear osmolarity values often reported in dry eye disease.

Dry Eye Disease

Pathophysiology and Clinical Presentation of Dry Eye Disease

Dry eye disease is among the most common disorders affecting the anterior eye.¹ Most often associated with the aging process (especially in postmenopausal women), dry eye also can be the result of lid or corneal defects, loss of lid tissue turgor, Sjögren syndrome, Bell's palsy, thyroid disorder–related eye disease, or various collagen diseases (e.g., rheumatoid arthritis) and has been associated with use of certain ocular and systemic medications.^{7–13} Dry eye disease has been generally classified by severity for a stepwise system of staged management and treatment recommendations, as follows: mild, for which step 1 (lower-level) interventions are appropriate; moderate, best managed with step 2 options; and severe, with step 3 and step 4 interventions (**Table 28–1**). This classification is imprecise, however, because characteristics of different severity levels can overlap, in accordance with the nature of this disease.^{10,11}

Table 28–1 Staged Management and Treatment Recommendations for Dry Eye Disease^{a–c}

Step 1: Mild Disease

- Education regarding the condition and its management, treatment, and prognosis
- Modification of local environment
- Education regarding potential dietary modifications, including use of systemic omega-3 fatty acid supplements (e.g., flaxseed oil)
- Identification and potential modification/elimination of offending systemic and topical medications
- Presence of ocular lubricants of various types (if MGD is present, consider lipid-containing supplements)
- Lid hygiene and use of warm compresses of various types

Step 2: Moderately Severe Disease

- If above options are inadequate, consider:
- Preservative-free ocular lubricants to minimize preservative-induced toxicity
- Tea tree oil treatment for *Demodex* infection (if present)
- Tear conservation
- Punctal occlusion
- Moisture chamber spectacles/goggles
- Overnight treatments (such as ointment or moisture chamber devices)
- In-office, physical heating and expression of the meibomian glands (including device-assisted therapies such as LipiFlow)
- In-office intense pulsed light therapy for MGD
- Prescription drugs to manage dry eye disease^d
- Topical antibiotic or antibiotic/steroid combination applied to the lid margins for anterior blepharitis (if present)
- Topical corticosteroid (limited duration)

- Topical secretagogues
- Topical nonglucocorticoid immunomodulatory drugs (such as cyclosporine)
- Topical LFA-1 antagonist drugs (such as lifitegrast)
- Oral macrolide or tetracycline antibiotics

Step 3: Severe Disease

If above options are inadequate, consider:

- Oral secretagogues
- Autologous/allogeneic serum eye drops
- Therapeutic contact lens options
 - Soft bandage lenses
 - Rigid scleral lenses

Step 4: Treatment-Resistant Disease

If above options are inadequate, consider:

- Topical corticosteroid for longer duration
- Amniotic membrane grafts
- Surgical punctal occlusion
- Other surgical approaches (e.g., tarsorrhaphy, salivary gland transplantation)

^a Potential variations within the disease spectrum are acknowledged to exist between patients, and the listed management options are not intended to be exclusive. Disease severity and etiology will dictate the range and number of management options selected from one or more step categories. Severity stages are relatively associated with the steps and are guidelines for treatment.

^b One or more options within a step category can be considered concurrently for each stage of disease. Options within a category are not ranked according to importance, and all may be equally valid.

^c Of note, the levels of evidence available to support the various management options differ and will inevitably be lower for newer management options. Thus, each treatment option should be considered in accordance with the level of evidence available at the time management is instigated.

^d The use of prescription drugs needs to be considered in the context of the specific clinical presentation and the relative level of evidence supporting their use for that indication, because these agents differ widely in mechanism of action.

Key: LFA-1 = Lymphocyte function–associated antigen-1; MGD = meibomian gland dysfunction.

Source: Reproduced with minor modifications from Jones L, Downie LE, Korb D, et al. TFOS DEWS II Management and Therapy Report. *Ocul Surf*. 2017;15:575–628. doi: 10.1016/j.jtos.2017.05.006.

The TFOS DEWS II report defines dry eye disease as “a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiologic roles.” Most people with symptoms related to ocular surface disease (OSD) suffer from a combination of abnormal meibomian gland physiology (i.e., evaporative dry eye disease) and tear underproduction (i.e., aqueous-deficient dry eye disease).¹⁰

Patients who have undergone refractive surgery may complain of transient dry eyes for weeks to months after the procedure. This effect usually is mild if it does occur, but it can be more pronounced in some patients. Drugs with anticholinergic properties (e.g., antihistamines, antidepressants), decongestants, diuretics, and beta blockers are some of the more common pharmacologic agents that may cause dry eye. The condition may be exacerbated by allergens or other environmental conditions (e.g., dry or dusty working situations), or by exposure to heating and air conditioning systems that reduce relative humidity, thereby increasing the evaporation of tears.

Dry eye disease typically is characterized by a normal-appearing white sclera or a mildly red eye, often associated with patient complaints of a sandy, gritty feeling or a sensation that something is in the eye. Contrary to what its name suggests, this condition often may manifest with excessive tearing initially. Abnormalities in the tear layer cause less-than-optimal lubrication of the ocular surface, with subsequent inadequate tear production and initiation of a vicious circle. Without proper and timely diagnosis and treatment, dry eye disease can eventuate in severe damage to ocular tissues, particularly the corneal surface (see [Color Plates](#), photograph 7). Evidence demonstrates that dry eye disease can be linked to a T cell-mediated inflammatory process, which can respond to treatment with immunomodulatory agents (e.g., cyclosporine).^{8–11}

Treatment of Dry Eye Disease

Early stages of dry eye disease often lend themselves to self-treatment, but as disease severity increases, medical intervention is required. Of note, however, patients with worsening disease often will continue with self-management interventions for step 1 as well as certain step 2 options, as listed in [Table 28–1](#), so the pharmacist should be aware of the potential for dangerous overtreatment in such instances.

Treatment Goals

The goal in treating dry eye disease is to alleviate the dryness of the ocular surface, thereby relieving the symptoms of irritation and preventing possible corneal and noncorneal tissue damage. Although this disorder also has been referred to as “dysfunctional tear syndrome” and “keratoconjunctivitis sicca,” the International Dry Eye Workshop (DEWS) has accepted *dry eye disease* as the most appropriate term.^{1,9} The DEWS I and the updated DEWS II reports, and the recently published preferred practice patterns from the American Academy of Ophthalmology have introduced an accompanying set of guidelines for treatment of dry eye disease.^{9–11}

General Treatment Approach

The primary modality of self-treatment for dry eye disease is the use of ocular lubricants. With disease of mild to moderate severity, however, treatment also may include other pharmacologic and nonpharmacologic recommendations, including patient education, environmental modifications, eyelid-specific therapies, elimination of offending topical or systemic medications, and use of systemic omega-3 fatty acid supplements (e.g., flaxseed oil) ([Table 28–1](#)). The availability of synthetic chemicals suitable for topical application to the eye led to the development of various solutions, so-called artificial tears, to help alleviate dryness of the ocular surface.

Artificial tears products vary by viscosity in accordance with the ingredients used in their preparation. With these products, higher viscosity allows more prolonged ocular contact time and greater resistance to tear dilution. Mild cases of dry eye disease may show improvement with less viscous products,

whereas more severe cases may require more viscous products. Bland (i.e., nonmedicated) ophthalmic ointments (e.g., petrolatum) or gels constitute another type of ocular lubricant. Because ointment preparations tend to cause blurred vision, they typically are reserved for use only at bedtime or for severe cases of dry eye. As with ointments, the more viscous the artificial tears are, the greater their blurring effect becomes. Vitamin A preparations also are available for treating dry eye disease. Specific guidelines for topical ophthalmic vitamin A require further study.

Nonpharmacologic measures (e.g., applying warm compresses, discontinuing any offending agents, maintaining good eyelid hygiene) also may increase eye comfort for patients with this disorder. Dietary modification including supplementation with omega-3 oils or flaxseed oil in the normal doses recommended by the manufacturer is thought to improve lid function, possibly because the products have some anti-inflammatory properties.⁹⁻¹¹

Eye care providers treat the most severe cases of dry eye disease with punctal plugs, which occlude the lacrimal drainage system to increase the available tear pool. Advances in understanding of the underlying pathophysiology of dry eye disease point to potential benefit from treatment with topical nonglucocorticoid immunomodulatory drugs (e.g., topical cyclosporine), topical lymphocyte function–associated antigen-1 (LFA-1) antagonist drugs (e.g., lifitegrast), topical corticosteroid (limited duration), and topical secretagogues.^{8,11} Whereas patients with mild dry eye disease may require only relief of ocular surface dryness, patients with moderate to severe disease may benefit from a combined approach incorporating immunomodulating agents (e.g., topical cyclosporine in conjunction with ocular surface lubrication). Accordingly, signs and symptoms suggestive of moderate to severe dry eye disease dictate referral to an eye care specialist.

Nonpharmacologic Therapy

The primary nondrug measure in self-care for dry eye disease is avoiding environments that increase evaporation of the tear film. If possible, patients should avoid dry or dusty places. Using humidifiers or repositioning workstations away from heating and air conditioning vents may help alleviate dry eye symptoms. In addition, avoiding prolonged use of computer screens and wearing eye protection (e.g., sunglasses, goggles) in windy, outdoor environments may further help alleviate dry eye problems.

Pharmacologic Therapy

Nonmedicated ointments are commonly used in treating minor ophthalmic disorders, including dry eye. Because ointments can cause blurred vision (resulting in severe visual limitations), combination therapy with a nonmedicated ointment plus artificial tears to help offset this undesired effect usually is recommended. Gels offer some clinical advantage in that they disturb vision less compared with ointments and are better tolerated by the patient. The effectiveness of retinol solutions for treating dry eye remains speculative.

Artificial Tear Solutions

Although many advances have been made in elucidating the mechanisms involved in tear film formation, the role of tears in maintaining a normal conjunctival and corneal surface is still not completely understood. Lubricants that are formulated as artificial tear solutions consist of preservatives, inorganic electrolytes to achieve tonicity and maintain pH, and water-soluble polymeric systems. The lubricating agents in artificial tears products are similar in palliative effect in that they all provide ocular lubrication, but buffering agents, preservatives, pH, and other formulation components may vary ([Table 28–2](#)). The newer artificial tear substitutes have important properties, including the ability to stabilize the tear film, protect the corneal and conjunctival cells, reduce tear evaporation with the incorporation of lipids, and enhance wound healing and lubrication of the ocular surface.^{1–3}

Table 28–2 Commonly Used Nonprescription Ophthalmic Lubricants

Trade Name	Primary Ingredient(s)
Artificial Tear Solutions	
Blink Tears, Mild to Moderate	Glycerin 0.3%; propylene glycol 1.0%; EDTA; hydrochloric acid; sodium hydroxide; BAK 0.01%
Bion Tears ^a	Hydroxypropyl methylcellulose 0.3%; dextran 70 0.1%
Clear Eyes Contact Lens Relief Drops	Sorbic acid 0.25%; EDTA 0.1%; NaCl; hydroxypropyl methylcellulose; glycerin
FreshKote PF	Polyvinyl alcohol 2.7%; povidone 2.0%

Trade Name	Primary Ingredient(s)
Lubricant Drops	
GenTeal Lubricant Eye Drops, Mild and Mild to Moderate	CMC; boric acid; phosphonic acid; NaCl; sodium perborate
Moisture Eyes ^b	Propylene glycol 1%; glycerin 0.3%; BAK 0.01%
Murine Tears Lubricant	Povidone 0.6%; PVA 0.5%; BAK
Nature's Tears Eyemist	Hydroxypropyl methylcellulose 2906 0.4%; KCl; NaCl; sodium phosphate; BAK 0.01%; EDTA
Oasis Tears	Glycerin 0.22%; EDTA; potassium sorbate; sodium chloride
Oasis Tears PF, Oasis Tears Plus	Glycerin (0.22%); sodium chloride; sodium hyaluronate
Ocucoat Lubricating ^b	Hydroxypropyl methylcellulose 0.8%; dextran 70 0.1%; BAK 0.01%
Preservative-Free Moisture Eyes ^a	Propylene glycol 0.95%; boric acid; NaCl; KCl; sodium borate; EDTA
Refresh Optive	CMC sodium 0.5%; glycerin 0.9%
Refresh Optive Advanced	CMC sodium 0.5%; glycerin 1%; polysorbate 80 0.5%
Refresh Optive Mega-3 PF	CMC 0.5%; glycerin 1.0%; polysorbate 80 0.5%; castor oil; flaxseed oil
Refresh Optive Repair	CMC sodium; glycerin 0.9%
Refresh Relieva Drops	CMC 0.5%; glycerin 0.9%
Refresh Tears	CMC sodium 0.5%; Purite ^c
Retaine HPMC Drops PF	Hypromellose (hydroxypropyl methylcellulose) 0.3%; citric acid; sodium citrate; sorbitol; water
Retaine MGD Emulsion	Novasorb; light mineral oil 0.5%; mineral oil 0.5%; tyloxapol USP; poloxamer 188; tromethamine; glycerol

Trade Name	Primary Ingredient(s)
Soothe	Restoryl (Drakeol-15 1.0% and Drakeol-35 4.5%); polysorbate 80 0.4%; octoxynol 40; NaCl; sodium phosphate; EDTA; polyhexamethylene biguanide preservative
Soothe PF	Restoryl (Drakeol-15 1.0% and Drakeol-35 4.5%); polysorbate 80 0.4%; octoxynol 40; NaCl; sodium phosphate; EDTA
Soothe XP, Soothe XP Preservative Free	Light mineral oil 1.0% emollient; mineral oil 4.5% emollient
Systane Complete	Propylene glycol 0.6%; boric acid; dimyristoyl phosphatidylglycerol; edetate disodium; hydroxypropyl guar; mineral oil; polyoxyl 40 stearate; Polyquad (polyquaternium-1) 0.001% preservative
Systane Balance	Propylene glycol 0.6%; boric acid; dimyristoyl phosphatidylglycerol; EDTA; hydroxypropyl guar; mineral oil; polyoxyl 40 stearate; Polyquad (polyquaternium-1) 0.001% preservative
Systane Lubricant Drops	PEG-400 0.4%; propylene glycol 0.3%; boric acid; calcium chloride; hydroxypropyl guar; Polyquad (polyquaternium-1) preservative
Tears Again	PVA 1.4%; dibasic sodium phosphate; EDTA; BAK 0.01%
Tears Naturale Forte	Dextran 70 0.1%; hydroxypropyl methylcellulose 0.3%; glycerin 0.2%; polyquaternium-1 0.001%; NaCl; KCl; sodium borate
Tears Naturale Free ^a	Hydroxypropyl methylcellulose 0.3%; dextran 70 0.1%
Tears Naturale II	Hydroxypropyl methylcellulose 0.3%; dextran 70 0.1%; Polyquad 0.001%
TheraTears PF ^a	CMC 0.25%
Nonmedicated Ointments	
Refresh Lacri-Lube ^a	White petrolatum 57.3%; mineral oil 42.5%; lanolin alcohols
Refresh PM ^a	White petrolatum 56.8%; mineral oil 41.5%; lanolin alcohols
Soothe Eye Ointment	Mineral oil 20%; white petrolatum 80%
Systane Lubricant Ointment	Mineral oil 3.0%; white petrolatum 94%; lanolin 3%
Nonmedicated Gels	

Trade Name	Primary Ingredient(s)
Blink Gel Tears	PEG 400 0.25%; boric acid; sodium chloride (OcuPure Brand) as a preservative; sodium hyaluronate
GenTeal Lubricant Eye Gel	Hydroxypropyl methylcellulose 0.3%; sodium perborate 0.028%; carbopol 980; phosphoric acid; sorbitol
TheraTears Gel	CMC 1%, KCl; sodium bicarbonate; NaCl; sodium phosphate
Refresh Celluvisc	CMC 1.0% single-use container
Refresh Liquigel	CMC 1.0%
Refresh Optive Gel	CMC 1.0%; glycerin 0.9%
Systane Gel Drops	PEG 400 0.4%; propylene glycol 0.3%; aminomethylpropanol; boric acid; edetate disodium; hydroxypropyl guar; Polyquad (polyquaternium-1) 0.001% preservative
Systane Lubricant Gel	Hypromellose (hydroxypropyl methylcellulose) 0.3%; carbopol 980; phosphonic acid; purified water; sodium perborate; sorbitol

^a Preservative-free product.

^b Preservative-free formulation available.

^c Stabilized oxychloro complex.

Key: BAK = Benzalkonium chloride; CMC = carboxymethylcellulose; EDTA = ethylenediaminetetraacetic acid; KCl = potassium chloride; NaCl = sodium chloride; PEG = polyethylene glycol; PVA = polyvinyl alcohol; USP = United States Pharmacopoeia.

One class of ophthalmic vehicles or ocular lubricants, in their commonly used ophthalmic formulation concentrations, is the substituted cellulose ethers, which include hydroxypropyl methylcellulose 0.3%–0.8% and carboxymethylcellulose (CMC) 0.5% and 1.0%. CMC 1% often is classified as a “gel” because of its higher viscosity. These solutions are colorless and vary in viscosity depending on the grade and concentration of the cellulose ether. Polyvinyl alcohol (PVA) 1.4%, povidone 0.6%–2.0%, polyethylene glycol 400,

propylene glycol 0.3%–0.6%, and glycerin 0.5%–1.0% are other vehicles commonly used as ocular lubricants.^{14–21} Carbomer polymers (e.g., Carbopol 980) often are added as inactive ingredients but may contribute to increasing viscosity, providing the “gel” component of artificial tears (e.g., GenTeal Severe Dry Eye). Sodium hyaluronate also is classified as an inactive ingredient, although some research suggests that it may promote healing of the corneal epithelium.¹⁴

Combining drugs with these vehicles increases overall viscosity, with consequent enhancement of the pharmacologic effects. The increased viscosity retards drainage of the active ingredient from the eye, thereby increasing the retention time of the active drug and enhancing bioavailability at the external ocular tissues. These effects generally are not accompanied by irritation or toxicity to the ocular tissues. Like the cellulose ethers, PVA also enhances stability of the tear film without causing ocular irritation or toxicity.

Povidone has surface-active properties similar to those of cellulose ethers. This compound is believed to form a hydrophilic layer on the corneal surface, mimicking natural conjunctival mucin. This mucomimetic property has firmly established the usefulness of povidone as an artificial tears formulation. Because this agent promotes wetting of the ocular surface, mucin- and aqueous-deficient dry eyes appear to benefit from its use.

An example of the most commonly recommended and newer products on the market is Refresh Optive Advanced Lubricant Eye Drops, which contains glycerin (0.9%), polysorbate 80 (0.5%), CMC 0.5%, boric acid, castor oil, erythritol, levocarnitine, and carbomer copolymer type A. This product is reported to be a lipid-based, triple-action preparation that helps lubricate and hydrate dry eyes and protects against evaporation of natural tears. Another product, Soothe, is an artificial tear solution that contains a lipid restorative layer, which provides a barrier to prevent loss of the aqueous component of the tears.

Many Systane products combine lubricants such as propylene glycol and/or polyethylene glycol with a gelling and polymer system. Hydroxypropyl guar binds to the hydrophobic corneal surface, forming a glycocalyx or gel-like environment that stays in contact with the ocular surface for a longer period. Systane is said to create an ocular shield, allowing epithelial repair that promotes patient comfort and relief of symptoms. Refresh Optive, a combination of CMC and glycerin, is believed to help protect the corneal epithelium through an osmotic protective effect.

Refresh Optive Mega-3 contains a blend of flaxseed and castor oils in addition to polysorbate 80, CMC, and osmoprotectants (glycerin, L-carnitine, erythritol, and trehalose) for corneal epithelial cell protection. Retaine MGD, Systane Balance, and Soothe XP all contain mineral oil for their lipid layers in addition to other lubricants.

Studies have shown that formulations of artificial tears products without preservatives are less likely than those with preservatives to irritate the ocular surface.^{7,10,13} Providers and patients should be aware, however, that preservative-free products should be discarded immediately after being opened and used. This precaution is needed because the remaining product in the opened container can readily become contaminated, potentially causing infection if applied to the ocular surface.

In most mild cases of dry eye disease, the patient instills drops of artificial tears once or twice a day, typically on arising in the morning and/or before retiring at night ([Table 28–3](#)).¹¹ A regimen of at least twice-daily drops is a good starting point. The viscosity of the drops and amount used can then be adjusted according to the patient's clinical response. For more severe cases, the dosage can be increased to 3–4 times daily. If the patient's clinical needs and response to therapy indicate the need for more frequent use, these solutions may be given as often as hourly. In many cases, use of artificial tears may be continued indefinitely, depending on patient response. Preservative-free products or those with less toxic preservatives (e.g., Purite [sodium perborate]) (see the section “Ophthalmic Preservatives”) are preferred in patients with moderate to severe dry eye disease or those who are sensitive to such agents.

Table 28–3 Administration Guidelines for Eye Drops

1. If you have difficulty determining whether eye drops have been successfully instilled into your eye, refrigerate the solution before administering it—the cold drops on the eye surface are easily detected. Do not refrigerate suspensions, however. Always check the expiration date.
2. Wash hands thoroughly. Wash areas of the face around the eyes. Contact lenses should be removed unless the product is designed specifically for use with contact lenses.
3. Tilt head back. When administering drops to children, have the patient lie down before placing drops in the eyes.
4. Gently grasp lower outer eyelid below lashes and pull eyelid away from eye to create a pouch.
5. Position dropper over eye by looking directly at it, as shown in the drawing.

6. Just before applying a single drop, look up.
7. As soon as the drop is applied, release the eyelid slowly. Close eyes gently for 3 minutes and position the head downward as though looking at the floor (using gravity to pull the drop onto the cornea). Minimize blinking or squeezing of the eyelid.
8. Use a finger to put gentle pressure over the opening of the tear duct.
9. Blot excessive solution from around the eye.
10. If multiple medications are indicated, wait at least 5 minutes before instilling the next eye drop preparation. This pause helps ensure that the first drop is not flushed away by the second and that the second drop is not diluted by the first.
11. If using a suspension, shake the container well before instilling. If using the suspension with another solution dosage form, place the suspension drop last because it has prolonged retention time in the tear film.
12. If both drop and ointment/gel therapy are indicated, instill the drops at least 10 minutes before the ointment/gel so that the ointment/gel does not present a barrier to the drops' penetration of the tear film or cornea.

FDA has warned the public about eye drop bottles with loose plastic safety seals or tamper-evident rings (i.e., collar or band), located below the bottle cap, which may fall onto the eye when the product is used. These devices are supposed to stay connected to the bottle neck. In some instances, a safety seal has dropped onto the user's eye when the bottle was tilted or squeezed. Such rings or seals should not be removed because of the potential to contaminate the tip of the dropper. FDA is identifying all relevant products and requires a revision to the packaging design that recommends a tamper-evident ring.²²

Use of ocular lubricants requires balancing the number of instillations (i.e., drops) per day with the viscosity of the recommended solution and the presence of a preservative. Specifically, as the daily dosage increases, toxicity from preservatives becomes more likely.^{7,13,16}

Although PVA is compatible with many commonly used drugs and preservatives, certain compounds—such as sodium bicarbonate, sodium borate, and the sulfates of sodium, potassium, or zinc— can cause solutions containing PVA to thicken or gel. For example, sodium borate is found in some extraocular irrigating solutions or irrigants and may react with contact lens wetting solutions that contain PVA.¹⁷ Therefore, a certain degree of caution is warranted in recommending solutions containing PVA.

Nonmedicated Ophthalmic Ointments

The primary ingredients in commercial nonprescription ophthalmic ointments ([Table 28–2](#)) are white petrolatum 60% (which contains a lubricant and an ointment base), mineral oil 40% (which helps the ointment melt at body temperature), and lanolin (which facilitates incorporation of water-soluble medications and also prevents evaporation).

The principal advantage of nonmedicated (bland) ointments is their longer retention time in the eye, which appears to enhance the integrity of the tear film. Therefore, mucin- and aqueous-deficient eyes can benefit from the application of lubricating ointments.

Ointment formulations usually are administered twice daily ([Table 28–4](#)). However, depending on the patient's clinical needs and therapeutic response, ointments may be administered as often as every few hours or only occasionally, as needed. Many patients prefer to instill the ointment at bedtime, to keep the eyes moist during sleep and to help prevent morning symptoms of dry eye.

Table 28–4 Administration Guidelines for Eye Ointments/Gels

1. Wash hands thoroughly. Wash areas of the face around the eyes.
2. If both drop and ointment/gel therapy are indicated, instill the drops at least 10 minutes before the ointment so that the ointment does not present a barrier to the drops' penetration of the tear film or cornea.
3. Tilt head back.
4. Gently grasp lower outer eyelid below lashes, and pull eyelid away from eye, as shown in the drawing.
5. Position ointment/gel tube over eye by looking directly at it.
6. With a sweeping motion, place a strip of ointment/gel, $\frac{1}{4}$ to $\frac{1}{2}$ inch wide, inside the lower eyelid by gently squeezing the tube, but avoid touching the tube tip to any tissue surface.
7. Release the eyelid slowly.
8. Close eyes gently for 1–2 minutes.
9. Blot excessive ointment/gel from around the eye.
10. Vision may be blurred temporarily. Avoid activities that require good visual ability until vision clears.

Because of the viscosity of the melted ointment base in the tear film, many patients complain of blurred vision with use of these products. This problem usually can be managed by decreasing the amount of ointment instilled or by administering the ointment at bedtime. Providers should routinely counsel patients to expect blurring of vision with use of eye ointments.

Ointment preparations generally are nonirritating, but preservatives can be toxic to ocular tissues. Some patients develop hypersensitivity reactions, which may prompt them to discontinue therapy. Changing to a single-use and/or preservative-free formulation (e.g., Systane Nighttime, Soothe Nighttime, Refresh PM) may eliminate symptoms associated with use of preservative-containing ointments. Preservative-free products are particularly helpful for use in long-term treatment. As a rule, pharmacists should recommend preservative-free, nonmedicated ointments for the treatment of dry eye to avoid the potential problems associated with preservatives. (See “Preservative-Free Formulations” under “Product Selection Guidelines.”)

Formulation Considerations for Ocular Lubricants and Other Ophthalmic Products

Ocular lubricants and other nonprescription ophthalmic products are formulated to reduce the stinging, burning, and other adverse effects commonly associated with some conventional ophthalmic drugs. With these products, lack of (or minimal) ocular discomfort on instillation is a major advantage, deriving from carefully controlled pH and the presence of buffers, tonicity adjusters, and preservative systems; patients are therefore more likely to adhere to recommended self-treatment regimens. Drug vehicle and preservative systems are among the most important inactive ingredients of these products. Other commonly used vehicles are dextran 70, gelatin, glycerin, hydroxyethylcellulose, methylcellulose, polyethylene glycol, and propylene glycol. Various other ingredients often are included as excipients (i.e., agents to improve tolerability and solubility of artificial tears).

Ophthalmic Preservatives

Preservatives are incorporated into multidose ophthalmic products. These components are intended to destroy or limit the growth of microorganisms inadvertently introduced into the product. Surfactants, one of two distinct groups of preservatives, usually are bactericidal, meaning that they disrupt the

bacterial plasma membrane. Of the quaternary surfactants, benzalkonium chloride (BAK) and benzethonium chloride are preferred by many manufacturers because of their stability, excellent antimicrobial activity, and long shelf-lives. Unfortunately, both agents can have toxic effects on the tear film and the corneal epithelium.^{7,18,19} Long-term use of topical products containing BAK can lead to damage of conjunctival and corneal epithelial cells. Complications associated with use of BAK-containing products include allergy, fibrosis, dry eye disease, and increased risk of failure of glaucoma surgery.^{7,20} Although only a small percentage of patients with dry eye disease experience BAK toxicity, this drawback may become quite problematic for those exhibiting symptoms. Polyquad, a high-molecular-weight quaternary compound, does not bind to contact lenses and may be less toxic than BAK.

Chlorhexidine is useful as an antimicrobial agent in the same range of concentrations as for BAK, yet it is used at lower concentrations in commercial ophthalmic formulations. Because it does not alter corneal permeability to the same extent as with BAK, chlorhexidine is not as toxic to the eye.

The second distinct group of preservatives includes the metals mercury and iodine, their derivatives, and alcohols. With the mercury-based preservatives, patients who become sensitized to thimerosal can develop contact blepharitis or conjunctivitis after several weeks of exposure and must discontinue the use of products that contain it. These products are rapidly disappearing from the marketplace.

Chlorobutanol is less effective than BAK as an antimicrobial preservative and, in fact, tends to break down in bottles during prolonged storage.^{17,18} However, prolonged use of chlorobutanol does not appear to produce allergic reactions. This preservative often is used in 0.5% concentrations and has both antifungal and antibacterial properties.

Methylparaben and propylparaben, both *p*-hydroxybenzoic acid derivatives, have a long history of use in some ophthalmic medications (especially in artificial tears and nonmedicated ointments). However, these preservatives are unstable at high pH and can sometimes induce allergic reactions.

Ethylenediaminetetraacetic acid (EDTA) is a chelating agent that preferentially binds and sequesters divalent cations. EDTA assists the action of thimerosal, BAK, and other agents but can sometimes induce contact allergic reactions.^{17,18}

Sodium perborate (e.g., GenAqua), which has been used extensively as a tooth-bleaching agent, has found a new use as an ophthalmic preservative. The first of two so-called disappearing preservatives, sodium perborate dissociates on contact with the eye to form hydrogen peroxide, which in turn rapidly dissociates to oxygen and water. The amount of hydrogen peroxide formed is so small that it does not produce eye irritation. The second disappearing preservative, a stabilized oxychloro complex (e.g., Purite, OcuPure), also is designed to dissociate on contact with the eye. After exposure to long-wavelength UV light, Purite breaks down quickly to water and sodium chloride. These disappearing preservatives have the advantage of microbial protection while potentially limiting preservative toxicity.

Other, less commonly used ophthalmic preservatives include cetylpyridinium chloride, phenylethyl alcohol, sodium propionate, and sorbic acid.

Ophthalmic Excipients

Other useful excipients are antioxidants, wetting agents, buffers, and tonicity adjusters. Antioxidants prevent or delay deterioration of products that are exposed to oxygen. Wetting agents reduce surface tension, allowing the drug solution to spread more easily over the ocular surface. Buffers are added to help maintain a pH range of 6.0–8.0, thereby preventing ocular discomfort on product instillation. Tonicity adjusters allow the medication to be isotonic with the physiologic tear film. Products in the sodium chloride equivalence range of 0.9%–1.2% are considered isotonic; use of these products helps limit ocular irritation and tissue damage. Solutions in the tonicity range of 0.6%–1.8% usually cause no discomfort when instilled in the human eye. Hypertonic solutions used for corneal edema are not well tolerated.

Product Selection Guidelines

Clinical results and patient acceptance remain the final criteria for determining a product's efficacy in the treatment of dry eye. Of importance, no single formulation has yet been identified that will universally relieve clinical signs and symptoms while maintaining patient comfort and acceptance.^{16,17} If symptoms do not subside after 72 hours of treatment, the patient should be encouraged to seek further assessment from an eye care specialist.

Preservative-Free Formulations

In recent years, artificial tears preparations have been introduced in preservative-free formulations and, more recently, in disappearing-preservative formulations. These preparations are beneficial for patients who are sensitive to preservatives such as BAK and thimerosal, those who use drops frequently, and those with compromised corneas. Products such as GenTeal (Mild to Moderate or Moderate to Severe), Refresh Optive, Refresh Tears, and lubricant gels such as Systane Lubricant Eye Gel and Tears Again Liquid Gel, are uniquely formulated to allow the preservative to rapidly dissociate into nontoxic components on the ocular surface. True preservative-free artificial tears preparations (e.g., Refresh Optive Advanced Preservative Free, Soothe Preservative Free, Blink Tears Preservative Free) are available in a variety of unit-dose dispensers. Some of these products are formulated to provide electrolyte support to the damaged surface epithelium of the eye. Preservative-free formulations not only are more expensive than preserved artificial tear solutions but also are easily contaminated during use. Therefore, patient counseling should emphasize the need to follow strict hygienic procedures for self-administration and to discard any unused product immediately after opening and using it.

Associated Lesions

Pingueculae are yellowish bumps, often located on the midportion of the sclera between the eyelids that is exposed to the sun. They are believed to be caused by UV light from the sun and exposure to dust and wind. Dry eye disease may contribute to enlargement or exacerbation of these lesions. Recommended treatment may include use of artificial tears to alleviate symptoms of dry eye, including itching, burning, and foreign body sensation. Wearing sunglasses to protect the eye from UV light, even on overcast days, also is recommended.

A *pterygium* is a benign, elevated growth, often triangular in shape, on the eye surface that typically starts on the sclera and continues to grow onto the cornea. These lesions also are believed to be caused by UV light from sun exposure, dust, and wind. Continued growth may cause ocular discomfort and blurry vision. Many patients may not experience symptoms or require treatment except in concert with symptoms seen with dry eye disease such as itching, burning, and dryness. Occasionally a pterygium can become inflamed,

with consequent hyperemia. Continued growth onto the cornea may even cause astigmatism and affect vision. Small pterygia often can be managed with use of artificial tears or lubricants. Reduced UV sunlight exposure with sunglasses and protection from dust and wind also are warranted. Larger lesions may be of concern because of their cosmetic appearance and/or may require surgical removal.

Allergic Conjunctivitis

Pathophysiology and Clinical Presentation of Allergic Conjunctivitis

The list of antigens that can cause ocular allergy is virtually endless, but the most common allergens include pollen, animal dander, and topical eye preparations. Patients with ocular allergy often report seasonal allergic rhinitis as well. Allergic conjunctivitis is characterized by a red eye with watery discharge (see [Color Plates](#), photograph 8). The hallmark symptom of ocular allergy is *pruritus* (itching). Vision usually is not impaired but may be blurred because of excessive tearing. Contact lenses should not be used until the allergic symptoms resolve.²³

Treatment of Allergic Conjunctivitis

Treatment Goals

The goals in treating allergic conjunctivitis are (1) to remove or avoid the allergen, (2) to limit or reduce the severity of the allergic reaction, (3) to provide symptomatic relief, and (4) to protect the ocular surface.²³

General Treatment Approach

Treatment often is directed at the root cause of the symptoms. Questioning the patient about exposure to allergens may help identify the offending substance. Removal or avoidance of the responsible allergen is the best

therapeutic strategy, but nonprescription ocular lubricants, ocular decongestants, ocular decongestant/antihistamine preparations, ocular antihistamine/mast cell stabilizer combination agents, oral antihistamines, and application of cold compresses will help relieve symptoms.^{24–28} Oral antihistamines often are used by patients with allergy symptoms; however, use of such agents has been associated with dry eye and can worsen the condition.

Nonpharmacologic Therapy

In addition to removing and/or avoiding exposure to the offending allergen, applying cold compresses to the eyes 3–4 times per day will help reduce redness and itching. Other important measures for avoiding the allergic response include checking the pollen count, keeping doors and windows closed, using hypoallergenic bedding, washing clothes frequently, bathing or showering just before bedtime, running the home's air conditioning system, using air filters, and so on. If eyes are itchy, cool compresses often provide some relief.^{24,29} Wearing sunglasses outdoors will shield eyes from the wind and allergens for many patients.

Pharmacologic Therapy

First-line treatment for allergic conjunctivitis is instillation of artificial tears (possibly refrigerated, in accordance with pharmacist recommendations) as needed (see [Tables 28–1](#) and [28–3](#)). Artificial tears may help wash out the allergens and provide some symptom relief.^{23,24} If symptoms persist, the patient should switch to an ophthalmic antihistamine/mast cell stabilizer or possibly a histamine type 1 (H₁) receptor antagonist product. The reclassification of products from prescription to nonprescription status has been a very favorable improvement for the treatment of allergic conjunctivitis. Ketotifen fumarate 0.025% (e.g., Zaditor, Alaway) is very safe and can be used in patients 3 years of age and older; it is dosed twice daily and is very effective in relieving the signs and symptoms of allergic conjunctivitis. As specified in the product name, Pataday Twice Daily Relief (olopatadine 0.1% solution) is dosed twice daily and Pataday Once Daily Relief (olopatadine 0.2% and 0.7% solution) once daily. Both are safely used in patients 2 years of age and older. Although a definite time period of treatment has not been well studied, the combination antihistamine/mast cell stabilizer products have been used for symptom management over many years. An oral antihistamine can be added to the

second treatment option, if needed. Medical referral is indicated if symptoms do not resolve after 72 hours of appropriate treatment.

Other nonprescription ophthalmic products designated specifically for treatment of allergic conjunctivitis include decongestants (often in combination with antihistamines) and, more recently, the antihistamine/mast cell stabilizer combination. (See [Chapter 11](#) for discussion of systemic nonprescription antihistamines and topical corticosteroids.)

Ophthalmic Decongestants/Alpha-Adrenergic Agonists

Five nonprescription decongestants are available for topical application to the eye: phenylephrine, naphazoline, tetrahydrozoline, oxymetazoline, and brimonidine. Decongestants reduce ocular redness by acting as local vasoconstrictors. In nonprescription ophthalmic products, phenylephrine is available in concentrations of 0.12% or lower. Higher concentrations of phenylephrine (2.5% and 10%) are prescription products and often are used for pupillary dilation. Naphazoline, tetrahydrozoline, and oxymetazoline are chemically classified as imidazoles. Higher concentrations of brimonidine at 0.1%–0.2% are used to lower intraocular pressure in open-angle glaucoma or ocular hypertension. These agents are available as solutions in a variety of concentrations ([Table 28–5](#)).

Phenylephrine acts primarily on alpha-adrenergic receptors of the ophthalmic vasculature to constrict conjunctival vessels, thereby reducing eye redness. The imidazoles also have greater alpha- than beta-receptor activity and are therefore clinically useful in constricting conjunctival blood vessels. These agents have only minimal effect on the underlying vessels of the episclera and sclera. Vasoconstrictors are effective in constricting conjunctival vessels, with consequent reduction in redness, vascular congestion, and eyelid edema, but they do not diminish the allergic response.^{24–28,30} [Table 28–6](#) lists dosages of ophthalmic decongestants.

When used as directed, ocular decongestants generally do not induce ocular or systemic adverse effects. However, presence of these products in households with young children and the use of such agents in this age group are risk factors that require patient education for prevention of adverse events. Ingestion of these agents can result in coronary emergencies and death. When used excessively or for other than brief periods, ocular decongestants

have the potential to produce rebound conjunctival hyperemia (i.e., rebound redness due to conjunctival congestion), allergic conjunctivitis, and allergic blepharitis.²⁵ Accordingly, they should not be used for more than 72 hours. Rebound congestion appears to be less likely with topical ocular use of naphazoline or tetrahydrozoline than with use of oxymetazoline or phenylephrine. Rebound congestion may be experienced within a few days of initiating treatment, and a case was reported within 8 hours of use.²⁵ Minimal rebound redness was reported with brimonidine 0.025% for 7 days on discontinuation after 4 weeks of treatment.²⁷ Patients with apparent rebound congestion should be referred to an eye care specialist for further evaluation and appropriate management.

Indiscriminate use of most decongestants in an irritated eye can induce papillary dilation and may precipitate angle-closure glaucoma in eyes that have narrow anterior chamber angles. Use of these products in angle-closure glaucoma is contraindicated, and health care providers should counsel patients with angle-closure glaucoma against using these products for treating allergic conjunctivitis.

Some patients may experience epithelial xerosis (abnormal dryness) from prolonged topical instillation of ocular decongestants, which may exacerbate the symptoms of irritation, pain, and dryness associated with allergic conjunctivitis.

Caution is warranted with use of ocular decongestants by patients with systemic hypertension, arteriosclerosis, other cardiovascular diseases, or diabetes. Adverse cardiovascular events also are possible when these agents are used in patients with hyperthyroidism.²⁶ Because of these possible adverse reactions, patients should not use phenylephrine and other ocular decongestants as ocular irrigants. During pregnancy, women should be advised to use ocular decongestants only sparingly, if at all. Instillation of solutions that have been stored at high temperatures has been associated with ocular reactions and severe mydriatic responses. In such cases, if signs or symptoms do not resolve within 72 hours, the patient should see an eye care specialist.

Brimonidine 0.025% (Lumify) is a recently approved nonprescription ocular decongestant for the treatment of ocular redness in adults and children older than 5 years. This selective alpha-2 adrenergic receptor agonist dosed at 4 times daily for 4 weeks was evaluated in a prospective, randomized, double-

masked, vehicle-controlled trial.²⁷ Brimonidine 0.025% was found to significantly reduce ocular redness, was not associated with tachyphylaxis, and exhibited rare rebound redness. Brimonidine 0.025% appears to be better tolerated than other decongestants, although controlled trials comparing the various agents have not been completed.

Ophthalmic Antihistamines and Ophthalmologic Antihistamine/Mast Cell Stabilizer Combinations

Two nonprescription antihistamines are available for topical ophthalmic use: pheniramine maleate and antazoline phosphate. Although either agent is effective alone, nonprescription products containing these antihistamines also contain a decongestant. The two combinations are pheniramine/naphazoline and antazoline/naphazoline ([Table 28–5](#)).

Table 28–5 Commonly Used Nonprescription Ophthalmic Products Containing Decongestants, Antihistamines, and/or Astringents

Trade Name	Primary Ingredient(s)
Decongestant Eye Drop Products	
Clear Eyes	Naphazoline HCl 0.012%; glycerin 0.25%; BAK
Clear Eyes Itchy Eye Relief	Naphazoline 0.012%; BAK; EDTA; zinc sulfate 0.25%; glycerin 0.2%
Lumify	Brimonidine tartrate 0.025%; BAK; boric acid; glycerin
Murine Plus for Dry Eyes	Tetrahydrozoline HCl 0.05%; povidone 0.6%; PVA 0.5%; BAK
Opti-Clear	Tetrahydrozoline 0.05%; BAK 0.01%; boric acid; EDTA; sodium borate; NaCl
Visine Advanced Relief	Tetrahydrozoline HCl 0.05%; PEG 400 1.0%; povidone 1.0%; BAK 0.01%; dextran 70, 1.0%

Trade Name	Primary Ingredient(s)
Visine Original	Tetrahydrozoline HCl 0.05%; BAK 0.01%
Antihistamine/Mast Cell Stabilizer Eye Drop Products	
Zaditor, Alaway	Ketotifen 0.025%; BAK 0.01%; glycerol; sodium hydroxide and/or hydrochloric acid; purified water
Pataday Twice Daily Relief	Olopatadine 0.1%; BAK 0.01%; dibasic sodium phosphate; HCl sodium hydroxide (adjust pH); purified water; sodium chloride
Pataday Once Daily Relief 0.2%	Olopatadine 0.2%; BAK chloride 0.01%; dibasic sodium phosphate; hydrochloric acid/sodium hydroxide (adjust pH); purified water; and sodium chloride
Pataday Once Daily Relief 0.7%	Olopatadine 0.7%; povidone; hydroxypropyl-gamma-cyclodextrin; polyethylene glycol 400; hydroxypropyl methylcellulose; boric acid; mannitol; BAK 0.015%; hydrochloric acid/sodium hydroxide (to adjust pH); purified water
Antihistamine/Decongestant Eye Drop Products	
Naphcon A	Pheniramine maleate 0.3%; naphazoline HCl 0.025%; BAK 0.01%
Opcon-A	Pheniramine maleate 0.315%; naphazoline HCl 0.02675%; hydroxypropyl methylcellulose 0.5%; BAK 0.01%
Visine-A	Pheniramine maleate 0.3%; naphazoline HCl 0.025%; BAK 0.01%
Decongestant/Astringent Eye Drop Products	
Clear Eyes ACR	Naphazoline HCl 0.012%; zinc sulfate 0.25%; glycerin 0.2%; BAK
Zincfrin	Phenylephrine HCl 0.12%; zinc sulfate 0.25%; BAK 0.01%
Zinc Sulfate Eye	Zinc sulfate 0.4%

Trade Name	Primary Ingredient(s)
Drops	

^a Preservative-free formulation.

Key: BAK = Benzalkonium chloride; EDTA = ethylenediaminetetraacetic acid; HCl = hydrochloride; NaCl = sodium chloride; PEG = polyethylene glycol; PVA = polyvinyl alcohol.

Pheniramine and antazoline are in different antihistamine classes, but both act as specific H₁ receptor antagonists.^{28–30} Topical antihistamines are used for rapid relief of symptoms associated with seasonal or atopic conjunctivitis. Using a decongestant with either of these topical antihistamines has been shown to be more effective than using either agent alone.^{28–30}

Ketotifen fumarate is a combination ophthalmic antihistamine/mast cell stabilizer. It has very potent H₁ receptor antagonist activity, thereby preventing acute histamine-mediated allergy symptoms. The mast cell stabilization activity inhibits mast cell degranulation, preventing the release of inflammatory mediators, including histamine. Ketotifen also inhibits eosinophils, which in turn inhibits the release of late-phase mediators. Ketotifen provides relief within minutes, its effects may last up to 12 hours from a single dose, and it does not contain a vasoconstrictor.^{24,28} It is therefore a very safe product, raising no concerns for vasoconstrictor overuse.

Another recently approved nonprescription combination antihistamine/mast cell stabilizer is olopatadine HCl. It is available in two formulations: Pataday Twice Daily Relief (olopatadine HCl ophthalmic solution 0.1%) is approved for the temporary relief of ocular itching and redness due to pollen, ragweed, grass, and animal hair or dander. Pataday Once Daily Relief (olopatadine HCl ophthalmic solution 0.2% and 0.7%) is approved for the temporary relief of ocular itching due to pollen, ragweed, grass, and animal hair or dander. These products were previously available for many years as prescription drugs and have proved to be very safe and effective.

Table 28–6 provides dosages of the antihistamine combination products. Burning, stinging, and discomfort on instillation are the most common adverse effects of ophthalmic antihistamines.^{24,28,30}

Table 28–6 Dosage Guidelines for Nonprescription Ophthalmic Decongestants and Antihistamines				
Agent	Nonprescription Concentration (%)	Dosage	Duration of Action (hours)	Duration of Use
Decongestant Products^a				
Phenylephrine	0.12	1–2 drops up to 4 times/day	0.5–1.5	72 hours
Naphazoline	0.1, 0.12, 0.02, 0.03	1–2 drops up to 4 times/day	3–4	72 hours
Oxymetazoline	0.025	1–2 drops every 6 hours	4–6	72 hours
Tetrahydrozoline	0.05	1–2 drops every 4 hours	1–4	72 hours
Brimonidine	0.025	1 drop up to 4 times daily	6–8	4 weeks
Antihistamine/Mast Cell Stabilizer^b Products				
Olopatadine	0.1/0.2	1 drop every 12 (0.1) or/24 (0.2) hours	12/24	>72 hours
Ketotifen	0.025	1 drop every 8–12 hours	8–12	>72 hours
Decongestant/Antihistamine Products				
Naphazoline/ pheniramine	0.025 (naphazoline)	1–2 drops 3–4 times/ day	3–4	72 hours
	0.3 (pheniramine)			
Naphazoline/ antazoline	0.05 (naphazoline)	1–2 drops 3–4 times/ day		72 hours
	0.5 (antazoline)			

^a U.S. Food and Drug Administration. Ophthalmic drug products for over-the-counter human use: final monograph. *Fed Regist.* 1958;53(43):7076–7092.

^b Zaditor [product insert]. Novartis Pharmaceuticals Corporation, East Hanover, NJ.

Ophthalmic antihistamines have anticholinergic properties and may cause pupillary dilation. This effect is seen most commonly in people with light-colored irises or compromised corneas (e.g., from contact lens wear).^{28–30} In susceptible patients, pupillary dilation can lead to angle-closure glaucoma. Therefore, these agents are contraindicated in persons recognized to be at risk for angle-closure glaucoma.^{28–30} Sensitivity to any of the components is another contraindication.

Product Selection Guidelines

After artificial tear solutions, ketotifen and olapatadine are the second safest and most effective products for the treatment of allergic conjunctivitis. Once- or twice-daily dosing and proven safety for use in children 2–3 years of age and older make either of these agents the primary option for self-treatment for signs and symptoms of allergic conjunctivitis.

Although product-to-product comparisons are available for decongestant and antihistamine ophthalmic products, definitive conclusions regarding clinical comparisons of the available nonprescription ocular decongestants are difficult to establish. Naphazoline 0.02%, however, is an excellent choice for nonprescription therapy for mild to moderate conjunctivitis of environmental, viral, or noninfectious origin because it can be soothing, reduces redness, and does not mask signs of infection if used for 72 hours or less.^{24,28,30}

Because rebound congestion appears to be less likely after topical ocular use of naphazoline or tetrahydrozoline, these agents generally should be recommended over phenylephrine or oxymetazoline.

Complementary Therapies

The homeopathic product known as Similasan Eye Drops #2 is indicated for

relief from itching and burning caused by allergic reactions. The active homeopathic ingredients are Apis, Euphrasia, and Sabadilla. The efficacy of this formulation has not been established in controlled clinical trials.

Corneal Edema

Pathophysiology and Clinical Presentation of Corneal Edema

Corneal edema may occur with any of a variety of conditions, including overwear of contact lenses, surgical damage to the cornea, and inherited corneal dystrophies. The edematous area of the cornea often is confined to the epithelium. Because the accumulated fluid distorts the optical properties of the cornea, subjective perception of halos or starbursts around lights (with or without reduced vision) is a hallmark symptom of corneal edema. An eye care specialist must diagnose this disorder before self-treatment is attempted.

Treatment of Corneal Edema

Treatment Goals

The goal in treating corneal edema is to draw fluid from the cornea, thereby relieving the associated symptoms.

General Treatment Approach

Once the diagnosis is established, patients can use topical hyperosmotic formulations to treat corneal edema. Of the topical ophthalmic hyperosmotic agents available, only sodium chloride can be obtained without a prescription in both solution and ointment formulations ([Table 28–7](#)). Sodium chloride is available as a 2% or 5% solution and as a 5% ointment. First-line treatment is instillation of a 2% solution 4 times per day. If symptoms persist for more than 1–2 weeks, nighttime use of a 5% hyperosmotic ointment should be added to the regimen.³¹ If symptoms do not abate after 1–2 weeks of the augmented

regimen, the patient should switch to a 5% hyperosmotic solution and continue nighttime use of the ointment. If symptoms still persist without relief after another 1–2 weeks, medical referral is necessary.³¹

Table 28–7 Commonly Used Miscellaneous Nonprescription Ophthalmic Products

Trade Name	Primary Ingredients
Hyperosmotics	
AK-NaCl Solution	NaCl 5%; methylparaben 0.023%; propylparaben 0.01%; boric acid; hypromellose (hydroxypropyl methylcellulose) 2906; propylene glycol
AK-NaCl Ointment ^a	NaCl 5%; lanolin oil; mineral oil; white petrolatum
Muro 128 Solution 2%	NaCl 2%; hydroxypropyl methylcellulose 2906; methylparaben 0.046%; propylparaben 0.02%; propylene glycol; boric acid
Muro 128 Solution 5%	NaCl 5%; boric acid; hydroxypropyl methylcellulose 2910; propylene glycol; methylparaben 0.023%; propylparaben 0.01%
Muro 128 Ointment ^a	Mineral oil; white petrolatum; lanolin
Irrigant Solutions	
Bausch + Lomb Eye Wash	Sodium borate; boric acid; NaCl; sorbic acid 0.1%; EDTA 0.025%
Bausch + Lomb Eye Wash Eye Irrigating Solution	Boric acid; sodium borate; NaCl; preserved with BAK chloride 0.01% in purified water
Collyrium for Fresh Eyes	Boric acid; sodium borate; BAK
Eye Stream	Sodium acetate 0.39%; sodium citrate 0.17%; sodium hydroxide and/or hydrochloric acid; BAK
Prosthesis Lubricant/Cleaner	
Enuclene Solution	Tyloxapol 0.25%; hydroxypropyl methylcellulose 0.85%; BAK 0.02%
TheraTears SteriLid Eyelid Cleanser	Water; PEG-80; sorbitan laurate; sodium trideceth sulfate

^a Preservative-free formulation.

Key: BAK = Benzalkonium chloride; EDTA = ethylenediamine tetraacetic acid; NaCl = sodium chloride; PEG = polyethylene glycol.

Pharmacologic Therapy

Hyperosmotics

Hyperosmotic agents increase the tonicity of the tear film, promoting movement of fluid from the cornea to the more highly osmotic tear film. Normal tear flow mechanisms then eliminate the excessive fluid. Many patients with mild to moderate corneal epithelial edema may experience subjective improvement in comfort and vision after appropriate use of these medications.

Usually, 1–2 drops of the solution are instilled every 3–4 hours ([Table 28–3](#)). The ointment formulation, however, requires less frequent instillation and usually is reserved for use at bedtime to minimize symptoms of blurred vision ([Table 28–4](#)). Because vision associated with corneal edema often is worse upon awakening, several instillations of the solution during the first few waking hours may be helpful.

In general, sodium chloride 5% in ointment form is the most effective product for reducing corneal edema and improving vision, but it tends to cause stinging and burning. For that reason, patients often prefer the 2% solution for long-term therapy. Hypertonic saline is nontoxic to the external ocular tissues, and allergic reactions are rare.³¹

The most important contraindication to the use of topical hyperosmotic sodium chloride is traumatic injury of the corneal epithelium. In such cases, this agent must not be given to treat associated corneal edema. The intact corneal epithelium permits only limited permeability to inorganic ions; therefore, an absent or compromised corneal epithelium will result in increased corneal penetration of the hyperosmotic product, reducing its osmotic effect.³¹ If the clinical history or the physical appearance of the eye suggests a damaged corneal epithelium, the affected person should be referred to an eye care specialist immediately. It is essential to warn patients

against preparation of homemade saline solutions for use in the eye because of the associated risk of infection.

Loose Foreign Substances in the Eye

Pathophysiology and Clinical Presentation of Loose Foreign Substances in the Eye

Despite the protective effect of the eyelids, foreign substances often contact the ocular surface. The immediate clinical manifestations are pain and watering (tearing). If exposure to the substance causes only minor irritation, with no abrasion of the eye surface, self-treatment is appropriate.³²

Treatment for Loose Foreign Substances in the Eye

Treatment Goals

The goal in treatment for loose foreign substances in the eye is to remove the irritant by copious irrigation. If a known foreign substance is a fragment of wood or metal, prompt attention from an eye care specialist is imperative because of the associated potential for penetrating injuries.

General Treatment Approach

If reflex tearing does not remove the foreign substance, the eye may need to be flushed. Lint, dust, and similar materials usually can be removed by rinsing the eye with sterile specific eyewash preparations (irrigants). Outside of a clinical setting, loose particles can be washed away by flushing the eyes with copious amounts of water from a sink faucet or even a garden hose. If needed, nonmedicated ophthalmic petrolatum ointment can be applied at bedtime.³² Ophthalmic petrolatum provides prolonged duration of protection, and the associated blurry vision does not pose a problem while the patient is sleeping.

Pharmacologic Therapy

Ocular Irrigants

An ocular irrigant is used to cleanse ocular tissues while maintaining their moisture; these solutions must be physiologically balanced with respect to pH and osmolality. Because the tissues that the irrigant contacts obtain nutrients (e.g., immunoglobulins, mucins) elsewhere, the role of irrigants is primarily to clear away unwanted materials or debris from the ocular surface. To reduce risk of contamination, patients should use ocular irrigants only on a short-term basis, and they should be alert to any further signs or symptoms that may point to other pathologic processes involving the eye. All ophthalmic irrigating solutions are available without a prescription ([Table 28–7](#)).

In the eye care provider's office, irrigating solutions are essential to certain clinical procedures, and they often are used to wash away mucous or purulent exudates from the eye. These solutions also are administered in the hospital setting to cleanse eye tissues between changes of ocular dressings.

Ocular irrigants should not be used for open wounds in or near the eyes. Patients should instead seek immediate medical attention and not place any solution in the eye. Although irrigating solutions may be used to wash out the eyes after contact lens wear, they have no particular value as contact lens wetting, cleansing, or cushioning solutions.

If the patient experiences unremitting eye pain, changes in vision, continued redness, irritation of the eye, or if the ocular condition persists or worsens, evaluation by an eye care specialist is strongly recommended. Irrigants may be packaged with an eyecup; however, because contamination of the eyecup is possible, it should never be used by anyone to rinse the eye.

Minor Eye Irritation

Pathophysiology and Clinical Presentation of Minor Eye Irritation

Nonallergic, minor eye irritation can be caused by a loose foreign substance in the eye, contact lens wear, or exposure of the eye to wind, sun (e.g., during snow skiing without protective eye goggles), smog, or chemical fumes including swimming pool chlorine. Redness of the eye is a common sign of minor irritation. In cases of snow blindness (i.e., temporary overexposure to light from the reflection off the snow), other burns from UV light (e.g., sunlamps), or arc welder's burns, common additional symptoms include pain and the subjective feeling of "sand in the eyes."

Treatment of Minor Eye Irritation

Minor irritation often responds well to instillations of artificial tear solutions or nonmedicated ointments (see "Treatment of Dry Eye Disease").

Zinc sulfate, a mild astringent, may be recommended for temporary relief of minor ocular irritation. The dosage is 1–2 drops up to 4 times daily.

The homeopathic product known as Similasan Eye Drops #1 is marketed to relieve dryness and redness caused by smog, contact lens wear, and other factors. The active homeopathic ingredients are Belladonna, Euphrasia, and Mercurius sublimatus. Controlled clinical trials have not demonstrated the efficacy of this formulation in the treatment of dry eye disease. This product is not approved by FDA.

Chemical Burn

Pathophysiology and Clinical Presentation of Chemical Burn

Chemical burns may occur from exposure to alkalis (e.g., oven cleaners, cement, lye), acids (e.g., battery acid, vinegar), detergents, and various solvents and irritants (e.g., tear gas, pepper spray, Mace). Chemical burns range in degree from mild to severe, depending on the inciting agent and/or exposure time. Patients complain of pain, irritation, photophobia, and tearing. Signs will vary according to the severity of injury. With less severe chemical burn injury,

clinical signs include superficial *punctate keratitis* (characterized by small pinpoint lesions associated with loss of epithelial cells in the cornea), perilimbal ischemia, chemosis, hyperemia, eyelid edema, hemorrhages, and concomitant first- or second-degree burns of the lid and outer skin. With more severe chemical burn injury, signs include corneal edema and opacification, anterior chamber inflammation, increased IOP, and retinal toxicity from scleral penetration. Alkali burns are more penetrating and potentially more damaging to eye tissues than acid burns. Alkali burns often are more resistant to irrigation and are associated with greater tissue destruction when they penetrate the deeper (stromal) layers of the cornea. If the burns are more superficial and only several layers of the corneal epithelium have been affected, the cells should be replenished within approximately 24 hours.³²

Emergency Treatment of Chemical Burn

Emergency treatment includes immediate copious irrigation with sterile ocular irrigants ([Table 28–7](#)), or with tap water if nothing else is available. Irrigation must be continued until an eye care specialist can be seen; if irrigation is stopped prematurely, residual material that may still be under the lid or in the inferior cul-de-sac may cause the pH of the tear film to revert to either acidic or alkaline.³² Further treatment after irrigation may include the use of cycloplegic agents, ophthalmic antibiotics, and analgesics. Most acid or alkali burns often are not treated with neutralizing solutions because it is difficult to determine the actual pH, which often continues to change; in such instances, overtreatment may cause even more severe injury. In more severe cases, if significant inflammation of the anterior chamber or cornea is present, ophthalmic steroids may be prescribed. Antiglaucoma medications also are used if the IOP is elevated. Follow-up evaluation and management by an eye care provider are required to prevent development of conjunctival adhesions and corneal complications. Chemical burns are considered ophthalmic emergencies, and patients with a history or clinical manifestations consistent with such injury should be immediately referred to an eye care specialist or hospital emergency department physician.

Artificial Eyes

Besides the obvious aesthetic benefits, clearing dried mucus or fluid secretions from the surfaces of artificial eyes eliminates a potential medium for bacterial growth. A sterile, isotonic buffered solution containing tyloxapol 0.25% and BAK 0.02% is available specifically for cleaning and lubricating ophthalmic prostheses. The primary method of preventing bacterial growth is routine hygiene with mild, nonallergenic soap and water.

Tyloxapol is a surfactant that softens solid matter on the prosthesis, and BAK aids tyloxapol in wetting the artificial eye. The solution is used in the same manner as for ordinary artificial tears. With the artificial eye in place, 1–2 drops of solution should be applied 3–4 times daily. In addition, the solution can be used as a cleanser to remove oil or mucus deposits; in this case, the artificial eye is removed, rubbed between the fingers and thumb, and then rinsed with tap water before reinsertion.

Contact Dermatitis of the Eyelid

Pathophysiology and Clinical Presentation of Contact Dermatitis of the Eyelid

Contact dermatitis of the eyelid can be a reaction to either an allergen or an irritant. Recognized etiologic factors include a change in cosmetics or soap, adverse effects of eye medications, and contact with other foreign substances. The involvement of both eyelids suggests allergy because such reactions typically follow general exposure rather than localized irritation. Common clinical manifestations include swelling, scaling, or redness of the eyelid, along with severe pruritus (itching). Sunburn of the eyelids and UV burn to the cornea (e.g., with recent sun exposure from beach or ski outings without eye protection; working in labs that use UV light; working with arc welding devices) should be ruled out.

Treatment of Contact Dermatitis of the Eyelid

Questioning the patient about the use of eye medications or new personal

care products (e.g., eyeliner, eye shadow) may help identify the offending substance quickly. Discontinuing use of the suspected product is the best treatment strategy. If swelling of the eyelid is marked, nonprescription oral antihistamines (e.g., diphenhydramine) along with application of cold compresses 3–4 times per day will help reduce the inflammation and itching.

Age-Related Macular Degeneration

Two types of age-related macular degeneration (AMD) are recognized: dry AMD and wet AMD. Dry AMD is more common, accounting for approximately 80% of all cases of this disorder. Wet AMD, of neovascular etiology, is significantly more sight-threatening and often is responsible for 80%–90% of those cases involving vision loss associated with AMD. Neovascularization, or new blood vessel growth, under the retina breaks through the retinal pigment epithelium (RPE) layer into the macula with consequent leakage of fluid and blood, causing macular edema and scarring. With the use of intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents to treat wet AMD, vision loss has been significantly stabilized; in many cases, vision has improved. Research on dietary supplementation for AMD in the Age-Related Eye Disease Study (AREDS) trials from the National Eye Institute (NEI) is reviewed next.

Dry AMD often is associated with retinal drusen, or groups of yellowish protein and debris seen when RPE cells lose some of their ability to function properly. Whereas symptoms of wet AMD are reported as distorted and wavy vision, reduced vision in one eye, and haziness or blurriness, patients with dry AMD may not exhibit any symptoms. Patients with a family history of AMD, cigarette smoking, older age (>50), and high cholesterol levels and heart disease and those with lightly pigmented skin are at greater risk for development of AMD and should have regular eye examinations for early detection. The recommendations for treating dry AMD include improved cardiovascular diet with green leafy vegetables, smoking cessation, and eye protection from the sun with polarized sunglasses. Use of a supplement with specific vitamins and minerals has been studied in two large clinical trials, AREDS and AREDS2, and demonstrated benefit in patients with intermediate- and late-stage dry AMD. Patients with early dry AMD did not demonstrate clinical benefit from use of the AREDS formulations. The AREDS and AREDS2 trials used nutritional supplements that may delay progression of intermediate to more advanced

AMD.^{33,34}

The AREDS formulations include vitamins C and E, zinc, copper, and the carotenoids beta-carotene (AREDS) and lutein/zeaxanthin (AREDS2). **Table 28–8** lists the specific ingredients and amounts of the products used in both trials. The vitamin and mineral doses are higher than the recommended dietary allowances (RDAs). Carotenoids are present in abundance in green leafy vegetables and are found at relatively low levels in animal-based foods. Beta-carotene is used to make vitamin A, which is required by the retina to detect light and convert it into “electrical,” or neural, signals. Of note, smokers were excluded from the AREDS trial because of the increased risk of lung cancer in smokers taking beta-carotene. Lutein and zeaxanthin replaced beta-carotene in the AREDS2 trial because beta-carotene itself is not found in the eye. Lutein and zeaxanthin are found in the retina and lens, where they are believed to act as natural antioxidants to help absorb damaging ultraviolet and blue light. This use of lutein and zeaxanthin has not been associated with increased cancer risk.

Table 28–8 Commercially Available (Nonprescription) Preparations of AREDS/AREDS2 Nutrient Formulations

Nutrient	AREDS Formula^a	AREDS2 Formula^b
Vitamin C	400 mg	400 mg
Vitamin E	400 IU	400 IU
Beta-carotene	15 mg	–
Copper (cupric oxide) ^c	2 mg	2 mg
Lutein	–	10 mg
Zeaxanthin	–	2 mg
Zinc	80 mg	80 mg

^a Not recommended for current or former smokers.

^b The nutrients used in AREDS2 formulations were provided by Alcon, Bausch + Lomb, DSM Nutritional Products Inc., and Pfizer.

^c Added to avoid zinc-related copper deficiency.

Key: ASRED = Age-Related Eye Disease Study; NEI = National Eye Institute.

Source: Adapted from NEI data. Available at: <https://www.nei.nih.gov/research/clinical-trials/age-related-eye-disease-studies-aredsareds2/aredsareds2-frequently-asked-questions>. Accessed June 8, 2020.

Zinc 80 mg (alone or in combination with antioxidant vitamins) was found to be of benefit in patients with AMD compared with a placebo. High concentrations of zinc in the original AREDS formula were associated with some gastrointestinal complaints. A lower dose of zinc was an option in the AREDS2 trial. No difference in the effects of zinc 80 mg versus 25 mg was found. Copper (cupric oxide) was added to the AREDS formulations to reduce the risk of copper deficiency anemia associated with high levels of zinc intake.

The AREDS formula contains 400 IU of vitamin E, which is above the usual RDA. Both AREDS trials, however, found no adverse effects attributed to this dose. Previous studies have demonstrated that more than 1500 IU/day from natural vitamin E (1100 IU/day for synthetic vitamin E) may be associated with an increased risk of bleeding. Some potential for vitamin E interactions with medications such as blood thinners, lipid-lowering drugs, and chemotherapeutic agents has been recognized. The AREDS trials found no effect of high-dose vitamin E on increased risk of prostate cancer. NEI recommends consulting with a health care provider before taking vitamin E or other nutritional supplements.

AREDS and AREDS2 supplements reduced the risk of developing intermediate to advanced AMD by about 25%. Neither of these formulations prevented the onset of AMD, nor did they have any effect on cataract formation. In the AREDS2 trial, lutein plus zeaxanthin or omega-3 fatty acids added to the AREDS formula had no additional overall effect on the risk of advanced AMD. No significant changes in effectiveness were correlated with use of the lower zinc concentrations in the AREDS2 trial. Among former smokers who took a formulation with beta-carotene in the AREDS2 trial, a higher incidence of lung cancer was demonstrated. Accordingly, beta-carotene was removed from the

formulation, and no significant change was subsequently noted in its effectiveness. Therefore, former and current smokers should take the AREDS2 formula and avoid beta-carotene, which increases the risk for lung cancer.^{33,34}

Diet alone will not provide the necessary nutrients to confer the same benefit obtained from the AREDS nutritional supplements. Patients are still advised to eat diets rich in green, leafy vegetables, which are a good source of lutein and zeaxanthin. Of interest, however, patients in the AREDS2 trial who had low levels of these nutrients in their diet benefited most from the preparation containing lutein and zeaxanthin. Participants had a 26% lower risk for progression to advanced AMD compared with those taking the original AREDS formula. Lutein and zeaxanthin are believed to offer similar or better protective benefits against advanced AMD compared with beta-carotene. Patients taking the AREDS formulation containing lutein and zeaxanthin but lacking beta-carotene demonstrated an 18% lower risk for progression to advanced AMD compared with those taking a beta-carotene product.^{33,34}

Comprehensive dilated eye examinations provide the best way to determine the risk for AMD risk, and genetic testing available as of June 2020 adds little to identifying this risk. NEI analyses of AREDS trials indicate that these formulations are beneficial for patients of all tested genotypes. The American Academy of Ophthalmology, however, does not support the use of genetic testing to guide treatment for AMD. More information is available from NEI at <https://www.nei.nih.gov/research/clinical-trials/age-related-eye-disease-studies-aredsareds2/aredsareds2-frequently-asked-questions>.

Patients currently taking a multivitamin preparation should check with their pharmacist to be sure there is no potential for interaction or too much overlap with the AREDS formulations. High-dose nutritional supplements can sometimes interfere with medications and compete with other vital nutrients for absorption into the body. People who are considering taking an AREDS formulation should make a list of all of their medications to share with their health care provider. The list should include supplements and nonprescription drugs. Before initiating any AREDS regimen, patients should consult with their regular health care provider or eye care specialist about which supplement, if any, is right for them.

Assessment of Ophthalmic Disorders: A Case-

Based Approach

For patients who have not seen an eye care specialist, the pharmacist or the primary care provider must determine whether the ophthalmic disorder is amenable to self-treatment or requires medical referral. Great care must be taken in assessing a patient with a new-onset, acute problem. Ocular inflammation and irritation can be caused by many disorders and conditions, some of which can be treated safely and effectively with nonprescription ophthalmic products. These products are used primarily to relieve minor signs and symptoms of burning, stinging, itching, and watering. FDA has suggested that self-treatment may be indicated for tear insufficiency, corneal edema, and external inflammation or irritation.

Cases 28–1 and 28–2 are examples of the assessment of two different patients presenting with ophthalmic disorders.

Table 28–9 describes the major features of disorders that necessitate medical attention. Any self-treatable condition that does not resolve within 72 hours constitutes an indication for immediate referral to an eye care specialist for further assessment.

Table 28–9 Differentiation of Ophthalmic Disorders/Conditions That Warrant Medical Referral			
Disorder/ Condition	Potential Signs/ Symptoms	Complications	Treatment Approach
Blunt trauma	Ruptured blood vessels, bleeding into eyelid tissue space, swelling, ocular discomfort, facial drooping	Internal eye bleeding, secondary glaucoma, detached retina, periorbital bone fracture (blowout fracture)	Medical referral is appropriate.
Foreign particles	Reddened eyes,	Corneal abrasions/ scarring, chronic red	Medical referral for removal of particles is appropriate.

Disorder/ Condition	Potential Signs/ Symptoms	Complications	Treatment Approach
trapped/ embedded in the eye	profuse tearing, ocular discomfort	eye, intraocular penetration from metal striking metal at high speeds	
Ocular abrasions	Partial/ total loss of corneal epithelium, blurred vision, profuse tearing, difficulty opening eye	Risk of bacterial/fungal infection with eye exposure to organic material, corneal scarring, anterior chamber rupture	Medical referral is appropriate.
Infections of eyelid/eye surface	Red, thickened lids, scaling, ocular discharge and matting of the lashes	Scarring of lids, dry eye, corneal abrasion or scarring, loss of vision, hordeolum (stye), chalazion (risk of malignancy—i.e., basal cell or sebaceous cell carcinoma), and blepharitis (loss of lashes, corneal irritation)	Medical referral is appropriate. In most cases, <i>hordeolum</i> (stye, internal or external) does not require more than warm soaks. Recurrence of hordeolum necessitates medical follow-up evaluation. <i>Blepharitis</i> often is a chronic problem that requires self-management with scrubs and warm soaks. Recurrence warrants medical referral.
Eye exposure to chemical splash, solid chemical, or chemical fumes	Reddened eyes, watering, difficulty opening eye	Scarring of eyelids and eye surface, loss of vision	To prevent/reduce scarring of eyelids from chemical burns, flush eye immediately for at least 10 minutes, preferably with sterile saline or water. If neither is available, flush with tap water. After flushing eye, arrange immediate transportation to an emergency care facility. No recommendation is noted for chemical neutralization.
Thermal injury to eye (welder's arc burn)	Reddened eyes, pain, sensitivity to light	Corneal scarring, secondary infection	Medical referral for definitive care (including possible eye patching) is appropriate.

Disorder/ Condition	Potential Signs/ Symptoms	Complications	Treatment Approach
Bacterial conjunctivitis	Reddened eyes with purulent, colored (mucous) discharge, ocular discomfort, eyelids stuck together on awakening	Typically, self-limited, with resolution in 2 weeks	Medical referral for treatment with topical antibiotics to clear infection more quickly is appropriate; some infections will require systemic antibiotic treatment.
Viral conjunctivitis	Reddened eyes with watery, clear, or white discharge, ocular discomfort, hyperemia, matting of the lashes	Typically, self-limited, with resolution in 2-3 weeks	If unresolved or condition worsens, medical referral may be necessary. Eye care specialist will monitor for corneal involvement. Treatment with topical decongestants to provide comfort is appropriate; cold compresses can be applied.
Chlamydial conjunctivitis	Watery or white or yellow mucous discharge, ocular discomfort, low-grade fever, possible blurred vision	Scarring	If infection with <i>Chlamydia</i> spp. is likely or confirmed, or if symptoms are too vague to rule out viral or allergic conjunctivitis, medical referral is mandatory.

Source: [Reference 32](#).

Case 28–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient states that she may have dry eye disease but believes it to be mild. She notes that dryness in both eyes becomes more severe as the day goes on. She also notices that during spring and fall her symptoms seem to get worse. She had some allergies to pollen and flowers when she was in her early teens but claims she had "grown out" of those. She has not used any eye drops except for an occasional artificial tears product for her dry eyes.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Symptoms usually occur during the spring when trees and flowers start to bud. She previously had ascribed her symptoms to a flare-up of her dry eye disease. In the past week, however, she has noticed some nasal congestion in conjunction with her dry eyes.
c. Description of the patient's efforts to relieve the symptoms	Artificial tears 3–4 times a day throughout the day. She would like to use some decongestant eye drops to "get the red out" because she has many sales meetings for which appearance is important, and she feels that her eye redness "gives a bad impression."
d. Patient's identity	Susan Lee
e. Patient's age, gender, height, and weight	46 years, female, 5 ft 6 in., 118 lb
f. Patient's occupation	Vice president of sales for a pharmaceutical company
g. Patient's dietary habits	Normal healthy diet with mostly fish and chicken. Occasional social drinking; works out on treadmill 6 times weekly.
h. Patient's sleep habits	Sleep schedule varies according to how busy she is at work;

	usually 6–7 hours a night.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	<i>Dry eye disease</i> (self-diagnosed), for which the patient uses an artificial tears product with lipid supplementation to mimic physiologic tears; tetrahydrozoline eye drops 3–4 times daily in both eyes.
j. Allergies	Previous history years ago of seasonal allergies to pollen and some flowers
k. History of other adverse reactions to medications	None
l. Other (describe) -----	n/a
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Patient is experiencing exacerbation of her dry eye condition. She also has occasional ocular pruritus that is not being controlled by her current therapy.
3. Identify exclusions for self-treatment (Table 28–8 and Figure 28–2).	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required and share this information with the patient or caregiver.	Options include (1) Refer Mrs. Lee to an eye care specialist (optometrist or ophthalmologist). (2) Suggest that Mrs. Lee discontinue her topical decongestant eye drops. Continue with her artificial tears as needed. Possibly switch to ketotifen topical drops twice daily for suspected allergy flare-up, especially during peak seasonal times. Occasionally use a different agent to “get the red out” to reduce risk of rebound congestion. (3) Take no action.
Plan	

5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	The patient prefers to discontinue her decongestant drops. She will increase her use of artificial tears to more frequent administration during the day as needed. She will start the new ocular antihistamine on days when her eyes are especially irritated. She did not realize that allergies can develop later in life. She will occasionally use a different agent to "get the red out" when she has a public presentation.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Instill 1 drop of the ketotifen product twice daily in both eyes." (See Table 28-3 .) "You do not need to use the drops if you do not notice any irritation, especially if you have not gone outside. Supplement throughout the day with the artificial tears product as needed, but wait at least 5 minutes after instilling the ketotifen eye drops." If she occasionally has a need for a topical agent for ocular redness, recommend instilling brimonidine 0.025% initially just before a meeting.
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"You may not need to see an eye care provider if you follow the recommended administration guidelines." (See Table 28-3 .)
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
a. Appropriate dose and frequency of administration	See Table 28-6 .
b. Maximum number of days the therapy should be employed	See Table 28-6 .
c. Product administration procedures	See Table 28-3 .

d. Expected time to onset of relief	See Table 28–6 .
e. Degree of relief that can be reasonably expected	“Complete symptom control should be possible. Some minor symptoms likely will appear from time to time.”
f. Most common adverse effects	“Transient burning, stinging, and discomfort may occur on instillation of the drops.” This has been reported with artificial tears, ketotifen, and brimonidine.
g. Adverse effects that warrant medical intervention should they occur	“If the eye pain worsens and the redness continues, see your eye care provider.”
h. Patient options in the event that condition worsens or persists	“An eye care specialist should be consulted if the condition does not improve, or if irritation and pain become intolerable.” She may wish to consult with an eye care specialist regarding her self-diagnosis of dry eye disease.
i. Product storage requirements	“Store product under cool conditions at less than room temperature and away from heat and light. Observe product expiration date.”
j. Specific nondrug measures	“Remove and/or avoid exposure to the offending allergen. Helpful measures can include ‘checking pollen count to guide outdoor activity, keeping doors and windows closed, running the home’s air conditioning, and using air filters.’ In addition, ‘apply cold compresses to the eyes 3–4 times a day to help reduce redness and itching.’”
Solicit follow-up questions from the patient or caregiver.	(1) “If my eyes still bother me, may I use the drops that I was using previously to get the red out?”
	(2) “Also, my spouse has prednisolone acetate eye drops that he used previously after his cataract surgery, and they seemed to help him very quickly. May I try his eye drops?”
Answer the patient’s or caregiver’s questions.	(1) “No. The ‘get-the-red-out’ eye drops actually can cause rebound worsening of the eye redness and dryness.” Note: In addition to causing rebound hyperemia, such products also are not recommended for patients with dry eye disease; limited use on the days of the worst symptoms is suggested.
	(2) “No. The prednisolone acetate eye drops, which are a steroid

	preparation, can cause significant eye complications, such as secondary infection, glaucoma, and cataract.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Encourage Mrs. Lee to contact you if she has any further questions.
Key: n/a = Not applicable.	

Case 28–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient’s symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient seeks your recommendation regarding her severe eye irritation. She states that about 30 minutes into a mountain hike on which she stopped to pick wildflowers, her left eye began to hurt and sting, with onset of light sensitivity. Also, a hiking companion noted that the eyelids looked swollen and red. Patient adds that about 30 minutes later, her right eye became affected with the same symptoms. The lids of both eyes are now swollen, and she is having trouble opening her eyes without stinging and pain on exposure to light. The pain and irritation in both eyes are significant. She wants to know what nonprescription product she could use to help relieve her symptoms and what other measures she should take for this problem.
b. Description of	The patient states that she experiences pain, tearing, and light sensitivity

any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	when she tries to open her eyes enough to see.
c. Description of the patient's efforts to relieve the symptoms	She just now returned from the mountain hike and has done nothing to relieve her symptoms. Patient expresses that she does not want to go to an "eye doctor" and requests your recommendations for appropriate self-care measures.
d. Patient's identity	Candice Bean
e. Patient's age, gender, height, and weight	20 years, female, 5 ft 5 in., 127 lb
f. Patient's occupation	Shoe store manager
g. Patient's dietary habits	Semivegetarian with limited meat consumption; generally chooses healthful foods.
h. Patient's sleep habits	Sleeps 6-8 hours a night; this varies with work duties.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	None
j. Allergies	None
k. History of other adverse reactions to medications	None
l. Other (describe) -----	Patient is an avid outdoor enthusiast; runs in marathons and sprint races.

Assess

2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Ms. Bean's eye symptoms are likely the result of an irritant or a foreign object that got into her eye during her hike.
3. Identify exclusions for self-treatment.	See Table 28–8 .
	<i>Ocular abrasions:</i> Partial/total loss of corneal epithelium, blurred vision, profuse tearing, difficulty opening eye. Risk of bacterial/fungal infection with eye exposure to organic material, corneal scarring, anterior chamber rupture. Medical referral may be appropriate if ocular irritant cannot be removed by self-treatment options or if symptoms are not relieved/worsen.
	<i>Foreign particles trapped/embedded:</i> Reddened eyes, profuse tearing, ocular discomfort. Risk of corneal abrasions/scarring, chronic red eye, intraocular penetration. Medical referral for possible removal of particles if present is appropriate.
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required and share this information with the patient or caregiver.	Options include (1) Take no action; wait to see if symptoms resolve on their own. (2) Thoroughly rinse/irrigate eyes to remove potential irritants still on the eye surface or trapped under lids. (3) Apply cold compresses as needed to control pain. (4) Use artificial tears eye drops for symptom relief. (5) Use a nonprescription combination antihistamine/mast cell stabilizer as needed to relieve itching and other allergy-related symptoms. (6) Take ibuprofen for control of pain.

	(7) Seek medical care if symptoms do not subside or resolve.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Ms. Bean is reluctant to see an eye care specialist. After being presented with a brief description of complications and risks, she decides to try a self-care approach, and then, if her eyes do not start to "feel better in a few hours," she will seek appropriate medical care.
6. Describe the recommended therapeutic approach to the patient or caregiver.	It is most likely that in touching the wildflowers, Ms. Bean experienced an irritant exposure to the left eye, followed by subsequent right eye exposure incurred by rubbing both eyes. She should rinse/irrigate both eyes with copious amounts of water to help remove possible irritants from the ocular surface. Additional self-treatment options include use of artificial tears, combination allergy drops, and ibuprofen and/or cold compresses for pain. If symptoms persist or do not resolve quickly, patient should seek medical attention for treatment, with the possibility of an embedded foreign particle.
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Seeing an eye care provider is the best option in your case. This specialist can determine what the irritant may be, whether there is a foreign particle embedded in the eye, how much damage has been done, and if additional treatment is required. Initially, however, you can use self-treatment options as recommended for possible irritant exposure, but if your symptoms are not relieved or worsen after a few hours, you should see an eye care specialist."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug	

therapy, convey accurate information to the patient or caregiver.	
a. Appropriate dose and frequency of administration	See Table 28–6 .
b. Maximum number of days the therapy should be employed	See Table 28–6 .
c. Product administration procedures	See Table 28–3 .
d. Expected time to onset of relief	See Table 28–6 .
e. Degree of relief that can be reasonably expected	“Complete symptom control should be possible. Some minor symptoms likely will appear from time to time until the condition has resolved.”
f. Most common adverse effects	“Burning, stinging, and discomfort may occur on instillation of the drops.”
g. Adverse effects that warrant medical intervention should they occur	“If the eye pain worsens or symptoms are not relieved in a few hours, see an eye care specialist.”
h. Patient options in the event that condition worsens or persists	“An eye care specialist should be consulted if the condition does not improve, or if irritation and pain become intolerable.”
i. Product storage requirements	“Store under cool conditions at less than room temperature and away from heat and light. Observe the product expiration date.”

j. Specific nondrug measures	“Remove and/or avoid exposure to the offending allergen. Helpful measures can include ‘checking pollen count to guide outdoor activity, keeping doors and windows closed, running the home’s air conditioning, and using air filters.’ In addition, ‘apply cold compresses to the eyes 3–4 times a day to help reduce redness and itching.’”
Solicit follow-up questions from the patient or caregiver.	“Is there anything I should do to prevent this in the future?”
Answer the patient’s or caregiver’s questions.	“In the future, wear sunglasses outdoors, and avoid touching organic materials and then rubbing your eyes.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Ask Ms. Bean to call you to report her status after initial self-treatment efforts. If she experiences no relief or worsening of symptoms, refer her immediately to an eye care provider.

Algorithm: Eye Surface Disorders

Figure 28–2 Self-care for eye surface disorders. Key: AH = Antihistamine; D/C = discontinue; MCS = mast cell stabilizer; OTC = over-the-counter.

Algorithm: Soft Lenses

Figure 28–3 Self-care for eyelid disorders. Key: AH = Antihistamine.

Patient Counseling for Ophthalmic Disorders

Before making treatment recommendations for a patient with an ophthalmic

disorder, the health care provider should carefully consider the nature and extent of the ocular involvement. In cases of acute and/or severe ocular disease, prompt evaluation (including establishing baseline visual acuity) for a specific diagnosis is essential before a self-management approach with use of nonprescription products can be considered. Some acute conditions (which may or may not involve ocular pain or blurred vision) can be appropriately treated with nonprescription agents, but a recent definitive diagnosis from an eye care specialist can give additional reassurance and confidence in recommending such treatment. Although the cost-effectiveness of ophthalmic care can be greatly improved using nonprescription agents, severe visual impairment—including blindness—can be a serious clinical and medicolegal complication if referral for evaluation and treatment is delayed. After careful consideration of the patient's history, the health care provider should always clearly identify the indications for and limitations of self-treatment. The algorithms in [Figures 28–2](#) and [28–3](#) can assist providers in recommending the appropriate measures for self-treatable disorders of the eye surface and eyelid, respectively.

Numerous nonprescription ophthalmic products for treating minor ocular irritations are available for self-administration by the patient with minimal or no supervision ([Tables 28–3](#) and [28–4](#)). These products also are adequate for treating certain clinical conditions diagnosed by primary care providers or eye care specialists. First-line therapy should always include counseling on nonpharmacologic treatment options. These interventions alone frequently are sufficient to relieve the ocular symptoms or are necessary as an adjunct to the ophthalmic drug therapy.

Proper drug instillation technique is critical if the target tissue (the eye) is to receive maximum benefit from the medication. Ophthalmic solutions and ointments often are used incorrectly. Carefully instructing patients in the proper self-administration procedures can help ensure maximum safety and effectiveness of these agents. Appropriate patient education and counseling must accompany dispensing of any ophthalmic product.

Although drug adverse effects and interactions are rare with topically applied ophthalmic products, the potential for such effects is well recognized. Accordingly, patients should be advised of the specific adverse effects, including the clinical signs of drug toxicity or allergy, associated with each of the products they are using.

The health care provider must actively assist patients in selecting the appropriate product, which will enhance compliance, minimize or avoid adverse effects, and reduce the attendant costs of therapy. The other major considerations in making therapeutic recommendations are whether the person has sensitivity to one of the product constituents, whether the product can be used with contact lenses, and whether the product has the potential to wash out prescription ophthalmic drugs the patient may be using. Except for ophthalmic antihistamines and decongestants, little product-to-product comparative research has been done for nonprescription ophthalmic preparations. Accordingly, therapy recommendations should be made on the basis of the patient's diagnosis and consideration of the products the patient is using. The box "Patient Education for Ophthalmic Disorders" lists specific information to provide in patient counseling.

Evaluation of Patient Outcomes for Ophthalmic Disorders

Patients who initiate self-treatment for allergic conjunctivitis, dry eyes, loose foreign substances in the eye, or minor eye irritation should see an eye care specialist if symptoms persist after 72 hours of appropriate treatment. The pharmacist may wish to schedule a follow-up interview with the patient to determine if the recommended treatment has provided adequate relief. Dry eye disease often is a chronic disorder, requiring regular use of ophthalmic lubricants. Patients with corneal edema should consult an eye care specialist if symptoms persist or worsen despite adherence to the recommended treatment regimen for the causative disorder.

Symptoms of contact dermatitis should resolve quickly once exposure to the offending substance is terminated. If symptoms persist after 72 hours of antihistamine use, referral for medical evaluation is warranted.

Patient Education for Ophthalmic Disorders

The objectives of self-treatment are (1) to relieve the symptoms of minor

ophthalmic disorders using appropriate nonprescription products or nondrug measures and (2) to use nonprescription products as directed for adjunctive treatment of ophthalmic disorders diagnosed by an eye care specialist. For most patients, carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

- Remove the offending agent/irritant responsible for your ocular condition or disease.
- If *blunt trauma* to the eye occurs, visit an eye care specialist for further evaluation as soon as possible.
- When making recommendations for topical ophthalmic products, assess the patient's ability to administer eye drops. Difficulty placing a drop in the eye may be associated with various limiting factors such as visual field loss, arthritis, essential tremor, Parkinson's disease, or altered cognition.
- If you have *dry eye disease* and the ophthalmic lubricants used for initial treatment are not effective, ask your eye care provider or pharmacist about the following therapeutic strategies: increasing the dosage, switching to a product with increased viscosity, and/or switching to a preservative-free product ([Table 28–2](#)).
- When treating *allergic conjunctivitis*, do not exceed the recommended dosages for ophthalmic antihistamine/mast cell stabilizer, decongestant, or antihistamine/decongestant products ([Tables 28–5](#) and [28–6](#)). Consult an eye care specialist if symptoms persist after 72 hours of treatment.
- Discard or replace eye drop bottles 30 days after the sterility safety seal is opened. The manufacturer's expiration date does not apply once the seal is broken.
- If *eye exposure to chemicals* occurs, irrigate the eye continuously for 10 minutes with copious amounts of water or an eye irrigant ([Table 28–7](#)) and seek immediate medical care.
- If a *loose foreign substance* such as lint, dust, or pollen enters the eye, flush the substance from the eye using an ocular irrigant or water ([Table 28–7](#)).
- If a *foreign object or substance* becomes embedded in the eye or trapped under the eyelid, see an eye care specialist for removal.

Continued presence of the substance could lead to an eye infection or tissue damage.

- Consult an eye care specialist before initiating self-treatment for *corneal edema*. If hyperosmotic solutions ([Table 28–7](#)) are recommended, follow the recommended dosages even though the product may sting. Continued utilization of these products will depend on the eye care specialist's recommendations.
- Note that taking ophthalmic vitamin supplements for macular degeneration along with general multivitamins may result in gastrointestinal upset or vitamin toxicity.
- If *contact dermatitis of the eyelid* occurs, wash the surrounding areas of the face, identify the cause of the reaction, and try to avoid future contact with the substance. Consult an eye care specialist if symptoms persist after 72 hours of use of oral antihistamines.

Key Points for Ophthalmic Disorders

- The pharmacist is well positioned in the community to assess for and treat various ophthalmic disorders, including medical referral as appropriate, or to recommend self-management with one or more nonprescription drugs.
- Many ophthalmic products are available to manage the symptoms of minor acute or chronic disorders and conditions of the eye and eyelid.
- Familiarity with the pathophysiology of certain ocular conditions and proficiency in the assessment of patients who present with such conditions will allow the pharmacist to optimize the safe, appropriate, effective, and economical use of nonprescription drugs to manage selected conditions of the eye and eyelid.
- Nonprescription ophthalmic products should be used only in cases of minor pain or discomfort. If the nature of the problem is in doubt, the pharmacist should refer the patient for medical care.

- Nonprescription ocular medications should not be recommended to patients who have demonstrated an allergy to any of the active ingredients, preservatives, or other excipients in the product.
- Patients who are already using a prescription ophthalmic product should use nonprescription products only after consulting with an eye care specialist or a pharmacist.
- Patients with narrow anterior chamber angles or narrow-angle glaucoma should not use topical ocular decongestants because of the risk of angle-closure glaucoma.
- Drug administration should be conservative in patients with hyperemic conjunctiva because of the potential for increased systemic drug absorption and the risk of adverse effects.
- The lowest effective concentration and conservative dosage frequencies should be used, especially for ocular decongestants; overuse should be avoided.
- Ophthalmic products frequently are used incorrectly; therefore, counseling on appropriate application of products is crucial.
- Patients should be evaluated by an eye care specialist to determine if they are candidates for an AREDS preparation for dry AMD. Consultation with the pharmacist is important if patients are taking other vitamin preparations.

Chapter 29: Prevention of Contact Lens-Related Disorders

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An estimated 40.9 million people use contact lenses in the United States, and more than \$8.5 billion is spent annually worldwide on contact lenses. Soft contact lenses, introduced in 1971, provide greater comfort than rigid lenses and account for >90% of lens purchases. In 2018, U.S. consumers spent \$3 billion on soft contact lenses.¹ The newest soft lens material, known as silicone hydrogel, continues to dominate this market category, being favored by 69% of soft lens wearers.¹

The types of lenses prescribed vary markedly among countries. Rigid gas-permeable (GP) lenses account for approximately 20% of prescribed contact lenses in some countries, such as France, New Zealand, and the Netherlands, and for 43% in Switzerland,² whereas only 6% of contact lenses prescribed in the United States are of the GP type.¹

Complications associated with contact lens wear are not uncommon, with reported rates of 23%–94%; this wide range is attributable in large part to variability in type of lens, wearing schedule, and adherence to the prescribed care regimen.³ Contact lenses, even when expertly fitted, induce local changes that alter ocular tissues and affect corneal metabolism. The prevention of contact lens–related disorders requires that both patients and health care providers understand the proper prescribing, fitting, and care regimens associated with safe contact lens wear. Failure to follow optimal practices can greatly increase the chances of development of corneal infection (with accompanying ulcers) and other ocular conditions that may result in permanent eye damage and blindness. Preventive measures aimed at improving patient hygiene and appropriate contact lens care and minimizing environmental factors, as well as adherence to recommended replacement frequency schedules, will reduce the overall risk of contact lens complications.^{3,4} Fortunately, most complications from contact lens wear are reversible, if attended to promptly. Approximately 23%–33% of patients discontinue wearing their contact lenses periodically or permanently, with lens discomfort or dryness cited as the most common reason.^{3,5,6} Silicone hydrogel contact lenses have the lowest discontinuation rates,⁶ and proper care and

fitting of lenses can help eliminate discomfort and encourage maintenance of an optimal wear schedule.

The fitting and dispensing of contact lenses, traditionally the sole domain of optometrists and ophthalmologists, underwent dramatic changes with passage of the Fairness to Contact Lens Consumers Act in 2003. This legislation requires that contact lens prescribers release a copy of the prescription to the patient at the conclusion of the fitting process, whether or not this information is requested.⁷ With prescription in hand, consumers can now purchase their contact lenses and related supplies from any of various authorized sources, including pharmacies—as well as nonprofessional sources for which appropriate training in eye care may be lacking. In 2018, 22% of all contact lens sales were conducted online.¹ It is unknown whether the source of contact lenses, such as online supplier versus eye care provider clinic, has an impact on the quality of eye care, including self-care. Some studies have found a lower likelihood of appropriate self-care^{8,9} and fewer eye exams when contact lenses are purchased online,¹⁰ whereas others have found no difference in complication rates.¹⁰ As detailed in this chapter, fitting and dispensing contact lenses involve more than specifying parameters for the lenses themselves. Additional considerations of importance include patient education regarding adherence to requirements for lens care systems, wearing schedules, and lens replacement schedules. Patient education also should incorporate proper lens handling and the signs and symptoms of complications as other essential aspects of a successful wear regimen. Another area of concern is the enforcement of expiration dates for lens prescriptions.

Use of Contact Lenses

Most people can wear one or more types of contact lenses without problems if certain precautions are taken. As detailed further on, however, in several specific instances the use of contact lenses is contraindicated.

Indications for Contact Lenses

Indications for the use of contact lenses include the correction of refractive errors such as myopia (nearsightedness), hyperopia (farsightedness), astigmatism, and presbyopia. In astigmatism, dissimilar curvatures of the refractive surface of the eye result in a blurred image. GP lenses or toric soft

lenses can be used to correct astigmatism.

The benefits of contact lens wear are widely known and include the convenience of freedom from eyeglasses, no obstruction to vision from eyeglass frames, no fogging of lenses caused by sudden temperature changes, improved optics and clarity of vision, wider peripheral field of vision, equal image sizes when refractive disparity exists between eyes, and better function during sports activities or exercise. Perhaps a significant reason for choosing contact lenses is the perceived improvement in self-image and personal appearance.¹¹

The decision to wear contact lenses rather than eyeglasses is sometimes based on therapeutic necessity or cosmetic interest. For example, in patients with keratoconus (a corneal dystrophy causing gradual protrusion of the central cornea), satisfactory vision usually is unattainable with ordinary eyeglasses but can be achieved with rigid contact lenses, which can favorably reshape the curvature of the cornea. Another example of therapeutic necessity is the use of soft contact lenses as “bandage” lenses in the case of severe corneal abrasions. Other, less common indications for contact lenses include aphakia (absence of the natural lens of the eye), corneal scarring, and disfigured eyes. In the first two conditions, patients typically see better with contact lenses, and for patients with disfigurement, tinted prosthetic soft contact lenses may improve cosmetic appearance by rendering defects from a variety of conditions virtually unnoticeable. Additionally, some patients utilize “special effects” contact lenses for cosmetic or occupational purposes, such as costume-related events, theatrical productions, or expression of personal style. These lenses often have a tint that hides the natural eye color and may add unique features to the appearance of the eye.

Contraindications and Warnings for Contact Lens Wear

Certain patients are poor candidates for contact lens wear—they either cannot or should not wear contact lenses. Contraindications often are based on lifestyle as well as on medical history. The following factors and conditions are relative contraindications that should be considered on an individual basis before the patient is fitted for contact lenses:

- Monocular vision. In persons with vision in only one eye, the risk of

complications such as inflammation or infection that can permanently scar the cornea in the seeing eye must be weighed against the need for optimal visual correction. Overnight wear of lenses should absolutely be avoided.

- Presence of an active pathologic process involving the lids, cornea, or conjunctiva. Such conditions include blepharitis, corneal infections (e.g., herpes, keratitis, *Staphylococcus aureus* infection, *Pseudomonas* infection), and conjunctivitis. Conjunctivitis associated with common colds or chronic allergic conditions such as hay fever and asthma also may make contact lens wear extremely uncomfortable or impossible.
- Presence of dry eye (keratitis sicca), except for use of “bandage” soft contact lenses for protection. Although this condition presents obvious difficulties for successful lens wear, it has been recognized that some patients with severe dry eye actually benefit from the use of bandage soft contact lenses to protect the ocular surface. In general, however, persons who have insufficient tear production, a deficiency or excess of mucin, or excessive lipid production and those who spend time in excessively dry environments may be unable to use contact lenses successfully. Poor blink rate or “incomplete” blinking (in which the eyelid does not completely close) also may contribute to difficulty with lens wear. Postmenopausal women may experience higher rates of dry eye, precluding successful contact lens wear.
- Pregnancy or use of oral contraceptives. The fluid-retaining effects of estrogen may lead to edema of the cornea, which will alter corneal topography and affect the fit of contact lenses.
- Diabetes. Patients with diabetes are advised against the use of continuous-wear contact lenses because of the retarded healing processes and reduced corneal sensitivity associated with their disease. These considerations probably are of lesser significance with daily-wear lenses, which often may be used unless specific problems arise (e.g., inflammation, infection, abrasion).
- Eye medications requiring frequent dosing (e.g., for treatment of glaucoma). The preservatives in multidose bottles can bind to soft contact lenses, with potential toxicity to the corneal epithelium.
- Personal habit, vocation, or hobby that is not conducive to lens wear (e.g., smoking, exposure to chemically toxic environments). Occupational conditions that may prohibit the wearing of contact lenses include exposures involving wind, glare, molten metals, irritants, dust and particulate matter, fur, dander, feathers, sand, tobacco smoke,

and chemicals and chemical fumes. Certain chemical fumes may be particularly hazardous because of the potential for concentration of irritants under a rigid lens or inside a soft lens. With lenses on the eye, contact of such substances with the cornea is potentially prolonged, which can lead to corneal toxicity.

- Medications that cause discoloration of fluids. Rifampin, used in therapy for tuberculosis, is a common offender.
- Activity (e.g., frequent air travel) that entails moving from a low to a high altitude. Such changes in altitude may induce hypoxia, with consequent edema of the cornea, or metabolic deficiency, resulting in irritation and corneal abrasions.
- A pattern of abusing lens wear or multiple episodes of ocular complications. The patient's medical history should be reviewed to identify potential problems.
- Inability to care for contact lenses appropriately. This restriction typically affects pediatric patients who are not properly supervised and older or impaired persons who lack cognitive skills or dexterity to handle contact lenses.

Soft Versus Rigid Contact Lenses

The three major categories of contact lenses are soft (hydrophilic), rigid gas-permeable (i.e., GP), and rigid non-gas-permeable (polymethylmethacrylate [PMMA]). PMMA lenses—often known as “hard” contact lenses—are rarely used today owing to their lack of oxygen permeability and are not discussed in this chapter. Soft and GP lenses are composed of single or multiple plastic monomers; soft lens materials contain water, but GP lens materials do not. Soft lenses are popular because of their excellent initial comfort on insertion. Rigid lenses, by contrast, have always provided the best optics, with consequent superior visual acuity. In the contact lens area of clinical practice, use of the term “hard lenses” during patient counseling is no longer acceptable because it creates a stigma about optimal lens designs for individual needs. Therefore, rigid lenses should simply be referred to as “gas-permeable lenses.” [Table 29–1](#) compares the advantages and disadvantages of soft and GP contact lenses with regard to lens properties, ease of care and handling, potential associated complications, and other characteristics.

TABLE 29–1 Advantages and Disadvantages of Soft and Gas-Permeable (GP) Contact Lenses

Soft Contact Lenses	GP Contact Lenses
Advantages	
Excellent initial lens comfort Rapid adaptation; well suited to intermittent lens wear Correction of nearly all forms of refractive error Ease of fitting Ease of care Trapping of foreign material under the lens unlikely Low likelihood of dislodging or falling out; well suited to use in sports activities Can be tinted for cosmetic or prosthetic purposes (many lenses have light tints to improve visibility when handling)	Excellent optics for optimal visual acuity Correction of nearly all forms of refractive error Improved vision for conditions with irregular corneas Fit customized to individual patient Economical Lower incidence of inflammatory/infectious complications
Disadvantages	
Less successful vision correction—achievement of excellent visual acuity not possible in all patients Fluctuations in vision due to variability in lens hydration with prolonged wear and changes in ambient temperature and humidity Lens fitting not customized to the patient's eye Greater likelihood of complications, especially from hypoxia Fragility and ripping (or tearing) of lenses during handling Susceptibility of lenses to adverse effects of preservatives in ophthalmic products Lack of surface markers on lens to verify correct eye once packaging is removed, with no means of distinguishing between lenses for left and right eyes	Longer initial adaptation period Capable of trapping foreign material beneath the lens, causing discomfort May dislodge from the eye More difficult to fit Subjective flare around the periphery that may be noticed at night, particularly with large pupils

Hydrophilic (Soft) Contact Lenses

First introduced in 1971, soft contact lenses have become the lens of choice from the standpoint of health care providers and patients alike, as mentioned previously. Soft contact lenses are now available in any spherical or cylindrical power, and they can correct for presbyopia, myopia, or hyperopia and astigmatism.¹²

In 1986, the U.S. Food and Drug Administration (FDA) classified soft hydrogel contact lenses into four categories according to water content and ionic properties: low water nonionic, high water nonionic, low water ionic, and high water ionic. Soft contact lenses with less than 50% water content are

considered to be in the low water categories. Less reactive surfaces are called nonionic, and more reactive materials are called ionic. Most eye care providers prescribe nonionic soft contact lenses because of their inherent chemical ability to deter the formation of charged protein and lipid deposits. Oxygen deprivation, or hypoxia, can be a common complication of contact lens use. The oxygen transmissibility of contact lenses is described by the term Dk/t ,¹² where D represents gas diffusion, k is the solubility coefficient, and t the contact lens oxygen transmissibility. A higher Dk/t value allows more oxygen to pass through the lens. As the water content increases, so does the k value, along with oxygen permeability. However, permeability also depends on lens thickness.

The original soft contact lenses were intended to be cleaned and disinfected daily and replaced on a yearly basis. Few patients could successfully wear these lenses, however, because of overall poor self-care compliance and higher complication rates.

Instead, today's disposable lenses represent greater than 97% of the soft lens market,¹ and having a fresh, clean lens available on a regular basis has lessened the incidence of complications from inadequate lens wear hygiene, such as contact lens-associated papillary conjunctivitis. These soft lenses are replaced monthly, biweekly, or daily, depending on how the specific lens is manufactured. The introduction of silicone hydrogel materials was a major factor in the emergence and availability of such continuous-wear lenses.

The eye care community was hopeful that frequent lens replacement would equate to improved general lens wear hygiene and sidestep the negative effects of biofilm development on the surface of lenses. Many eye care providers also believed that the use of silicone hydrogel materials would effectively eliminate inflammatory and infectious complications of contact lens wear, including microbial keratitis, by preventing or limiting hypoxia and its damaging effects on the corneal epithelium. Although years of clinical use have shown that these materials do in fact diminish the hypoxic effects of lens wear, such as redness, limbal neovascularization, and microcystic edema, they have failed to completely eliminate infectious and inflammatory complications.³ Continuous-wear contact lenses carry a higher risk of complications, such as corneal lesions.³ Patients should be made aware of these risks, and some prospective users may discover that they cannot tolerate continuous-wear regimens (for either 7 or 30 days, as approved by FDA for

specific products). None of the soft contact lenses on the market, including the silicone hydrogel types, can prevent or protect the eye from inflammatory and infectious complications. The importance of patient education regarding adherence to lens care regimens and wearing and replacement schedules, as well as awareness of more serious signs and symptoms, cannot be overemphasized to ensure safe contact lens wear.

Even a disposable, continuous-wear lens can be used on a daily-wear basis, and patients should replace lenses at the prescribed interval. When used on a daily-wear basis, these lenses must be cleaned and disinfected regularly. Patients looking to optimize convenience without exposing themselves to the risks associated with continuous wear should be directed toward daily disposable lenses. Daily disposables have the following advantages: (1) each lens is sterile before removal from its package for immediate insertion into the eye; (2) no cleaning regimen is necessary because the lens is discarded after wear for a day; (3) deposit formation is minimal; and (4) lens-related problems such as giant papillary conjunctivitis or allergic reactions to lens care solutions occur less frequently.

Hydrophilic Lens Fitting

Unlike with rigid contact lenses, which typically are custom-designed, the parameters of the most commonly used soft contact lenses are predetermined by the manufacturer and are proprietary in nature. Often, the lens diameter and base curve are limited to one or two choices at most, providing little flexibility for adjusting fit. Thus, if a lens does not fit correctly or causes some other complication, another lens design must be tried. Some exceptions are available, and custom-fitted soft lenses with a specified diameter, base curve, and power can be ordered.

Hydrophilic Contact Lenses as Therapeutic Devices

Aside from the cosmetic use of contact lenses, hydrophilic lenses have found wide application in the treatment of ocular disease and are being investigated for potential use as ocular drug delivery devices. Of note, hydrophilic lenses are employed as an “eye bandage” to protect the cornea and to promote corneal reepithelialization after corneal injury or various corneal surgical procedures. Some soft contact lenses are currently approved by FDA for use therapeutically as such bandage lenses in the treatment of corneal abrasions and other ocular

surface problems. It is important to counsel patients who are prescribed contact lenses for this purpose to be diligent in cleaning and disinfecting the lenses.¹³

Gas-Permeable Contact Lenses

Rigid contact lenses preceded soft lenses in the market but were quickly surpassed because of one primary factor: the greater initial awareness of rigid lenses on the eye. In terms of optical quality, rigid lenses are far superior to soft lenses. However, patients are willing to sacrifice clarity for comfort. In defense of rigid lenses, initial discomfort can dissipate over several weeks as adaptation occurs and nerve endings on the inner surface of the eyelids become desensitized to the presence of the lens.

Rigid GP lenses are made from monomer components of hydrophobic plastic compounds that allow oxygen to diffuse through the lens.¹² Advantages of GP lenses over soft contact lenses include increased oxygen transmissibility, reduced lipophilicity (e.g., less contamination from the environment), and sharper vision. These lenses also have less surface reactivity, thereby decreasing tear film deposits. Another significant advantage of GP lenses over soft contact lenses is a lower incidence of adverse inflammatory or infectious consequences. When properly cared for, GP lenses also are durable and can be reused repeatedly for months to years before replacement is necessary, making them more economical than soft lenses. Moreover, surface scratches and deposits can be removed with powerful cleaners or in-office polishing machines. The disadvantages of GP lenses include lesser surface wettability; a negative surface charge, which can attract lysozymes and other positively charged deposits; and greater mass, which can affect lens fit, depending on the specific type of lens.

GP lenses are the lens of choice for dealing with complicated corneal disorders such as keratoconus or corneal scarring from disease or trauma, and for use with transplanted corneas or those with high degrees of astigmatism. Unlike soft lenses, which drape over the surface of the cornea, even if it is irregular, rigid lenses create a new refracting surface, with a tear layer filling the gap between lens and cornea. GP lenses are available in a wide range of designs, including toric lenses for astigmatism and bifocals for presbyopia. Although far more limited in terms of choice, some GP materials also are FDA approved for either 7 or 30 days of continuous wear, depending on the material.

Gas-Permeable Lens Fitting

Most providers who prescribe contact lenses agree that compared with soft lenses, fitting GP lenses requires a higher level of both art and science. Unlike soft lenses, GP lenses are not mass-produced but rather are custom-designed and manufactured on demand, requiring the prescriber to specify the parameters of diameter, base curve, power, and material to order a lens.

Specialty Contact Lenses

Numerous companies manufacture soft contact lenses. The product offerings of many companies overlap to address the most common myopic, hyperopic, and astigmatic refractive errors. Many companies sell prepackaged, mass-produced lenses that consumers can buy in bulk with a prescription. Some offer customized lenses to address unusual needs. Several companies promote materials that absorb ultraviolet light. Corrective tinted lenses are available for easier handling and for cosmetic purposes. Translucent tints facilitate handling by increasing the visibility of the lens and also enhance eye color. Opaque lenses cover the iris and hide its natural color. These lenses also may be used as a prosthesis to mask corneal scarring. By contrast, all GP lenses are custom-made by laboratories that often use proprietary, computer-generated lens designs. These unique designs are aimed at specialty needs such as with keratoconus, post–corneal transplantation, corneal scarring, post–refractive surgery, aphakia, or high degrees of astigmatism.

Two specialty lenses worth mentioning are lenses for presbyopia and hybrid lenses. *Presbyopia* is the loss of accommodation in the aging eye, typically beginning around the age of 40 years, requiring the addition of plus power (i.e., adjustment for farsightedness) to improve the clarity of vision at a near reading distance. It affects people who are nearsighted or farsighted or who have an astigmatism and thus is common in contact lens wearers. In eyeglasses, a separate portion of the spectacle lens at the bottom of the lens provides this additional plus power for reading (bifocal glasses). This change in power is more difficult to accomplish with contact lenses. A common method of correcting presbyopia with contact lenses is monovision, a technique that uses standard lenses, fitted to the dominant eye corrected for distance and to the other eye corrected for near vision. Monovision can be effective, but it can affect depth perception, intermediate-distance vision, and night driving. Today, multifocal contact lenses are being designed to provide binocular vision for

patients, which provides a smooth transition among the near, intermediate, and far zones of the lens. The practitioner should discuss the options with the patient to determine what would work best for personal preferences or lifestyle requirements.¹⁴

A *hybrid contact lens* is a unique contact lens that combines GP and soft lens materials in the same lens. The overall advantages of this lens are excellent optics through the GP portion of the lens, improved comfort from the soft lens portion, greater oxygen permeability (compared with an earlier version of the lens), and accommodation for astigmatism and irregular corneas (e.g., with keratoconus or post–corneal transplantation). The disadvantages are expense, difficulty with insertion and removal, longer fitting time, and complications of lens wear. The care of these lenses follows the patterns described for soft contact lenses in later sections.

Algorithm: Soft Lenses

FIGURE 29–1 Basic care regimen for soft contact lenses. Key: UVR = Ultraviolet radiation.

Considerations for Lens Care

The manufacturing and marketing of contact lenses are regulated by the FDA ophthalmic devices division.¹⁵ Patients who wear contact lenses should use only lens care products that have been FDA-approved for use with their specific contact lenses.

The basic considerations for a well-formulated contact lens solution include pH, viscosity, isotonicity with tears, stability, sterility, and provisions for maintaining sterility (bactericidal action). The pH range of comfort is not well defined, because although normal tear pH is 7.4 (with a range of 6–8), values vary among individual patients. Accordingly, many contact lens solutions are formulated with pH values above or below 7.4 to prioritize stability and also to provide comfort. Solutions from different manufacturers should not be mixed because a precipitate may form.¹⁶

Soft Contact Lens Care

The goals of cleaning a contact lens are (1) to physically remove debris from the lens surface through the mechanical action of rubbing the lenses between the thumb and finger; (2) to prevent the accumulation of proteins from the tear layer on the lens; and (3) to disinfect the lens of organisms that can bind to the lens surface and potentially lead to infection. Lens disinfection is a crucial step, although all steps must be completed on a daily basis or after each wearing period to avoid ocular complications.¹⁷ The basic care regimen for soft lenses (Figure 29–1) differs from that for GP lenses.

Product Selection Guidelines

Since the early days of contact lens use, separate solutions have been available for each step of cleaning, rinsing, disinfecting, storing, and protein removal. These solutions include surfactants for cleaning the lens surface, saline solution for rinsing, disinfecting agents for sterilization, and enzyme-based products for protein removal, in addition to wetting drops for use while lenses are on the eye. To improve convenience and compliance, multipurpose products are available that combine these active ingredients in a biocompatible solution buffered for pH balance for use directly in the eye. Some of these solutions also contain demulcents to increase lubrication and comfort of the eye. Table 29–5 lists examples of products designed specifically for soft contact lenses

Tables 29–2 and 29–3 present detailed steps for cleaning soft contact lenses.

TABLE 29–2 General Cleaning Procedures for All Lens Types

- Before handling lenses, wash hands with noncosmetic soap and rinse thoroughly; then dry with a lint-free towel.
- Clean contact lenses only with commercially manufactured products made specifically for that type of lens. Homemade cleansers can scratch and contaminate the lenses or cause eye irritation, infection, or injury.
- Do not mix contact lens care products from different manufacturers unless an eye care provider confirms that the products are compatible.
- During cleaning, check lenses for scratches, chips, or tears and for the presence of foreign particles, warping, or discoloration. Also, ensure that lenses are clean and thoroughly rinsed of cleanser. Any residual impurities could cause eye discomfort.
- When cleaning a lens, rub it in a back-and-forth, rather than a circular, direction, even if

using a no-rub solution.

- Discard cleansers and other lens care products if the labeled expiration date has passed.
- Avoid touch contamination of open product bottle tips.

TABLE 29–3 Specific Cleaning Procedures for Soft Lenses

- Clean regular soft lenses daily with a surface-active cleaner at the end of daily wear.
- Clean continuous-wear soft lenses with a surface-active cleaner after each wearing.
- Place several drops of a cleaning product on the lens; gently rub the lens with the tip of the forefinger against the palm of the opposite hand, for 20–30 seconds, even if using a no-rub product, to ensure removal of protein deposits.
- Avoid cutting the lens with a fingernail or scratching the lens surface with grit or dirt on the hands.
- Rinse lenses with a sterile isotonic buffered solution. Never use tap water, because it is not isotonic and contains harmful microorganisms.
- Clean lenses at least weekly (or every day if using a daily product) with enzymatic cleaners, either separately from disinfection or as part of the disinfecting process.
- When combining enzymatic cleaning and disinfecting of the lenses as one step, see [Tables 29–5](#) and [29–8](#) for the appropriate products.
- Discard any enzyme cleaner that is discolored.

Soft Lens Disinfection

The lens care regimen must be built primarily around the use of a disinfecting system. In patient education, emphasis must be placed on hand hygiene and adherence to the manufacturer’s requirements for each disinfecting system, while stressing the minimum soaking time for disinfection.

Preservatives.

The most important point in considering contact lens disinfection pertains to the preservatives used both to keep multiuse solutions sterile and to disinfect the lens. A variety of preservatives that have effective antimicrobial properties are used. Daily use of the same bottle of any contact lens solution over a long period of time increases the risk of bacterial contamination. The solution must therefore contain a bactericidal agent that is both effective over the long term and nonirritating to the eye with daily use. Despite the presence of preservatives, once opened, any contact lens solution not used within the recommended time frame on the label, typically 1–3 months, must be

discarded. Touch contamination of the bottle tip also is a major concern, and if this occurs, it is imperative to dispose of the bottle. Patients should be directed to write the date on which the container is opened on the outside of the bottle.¹⁸

Disinfecting Methods.

FDA recommends disinfecting soft contact lenses before each reinsertion.^{17,18} Chemical-based disinfection is by far the most popular (Table 29–4). Thermal, or heat, disinfection is no longer a viable method of caring for today’s soft contact lenses. The alternative is an electronic system, PuriLens, that uses subsonic ultrasound agitation for cleaning and high-intensity ultraviolet light for disinfection. In chemical disinfection, lenses are stored for a specified period (usually 4–6 hours) in a solution containing bactericidal agents that are compatible with soft lens materials. Two basic chemical disinfection methods are available in the United States: chemical disinfectant systems and hydrogen peroxide–based systems.¹⁷ The first group uses the original chemical disinfecting solutions, which consisted of antimicrobial preservatives at sufficient concentration in storage solutions composed primarily of saline. Manufacturers currently are marketing solutions with less-sensitizing disinfectants for soft contact lens care. Examples are quaternary ammonium compounds (e.g., polyquaternium-1), biguanides (e.g., polyhexanide, polyaminopropyl biguanide), and amidoamine (e.g., myristamidopropyl dimethylamine). Modern chemical disinfectants have been found to be effective and are most commonly used.^{17,19}

TABLE 29–4 Guidelines for Disinfecting Gas-Permeable and Soft Lenses

Chemical Disinfection with Hydrogen Peroxide

- Using the cup provided with the hydrogen peroxide product, soak lenses for the length of time specified by the manufacturer. Do not use lens cups or cases supplied with other products.
- To disinfect and neutralize in one step, place platinum catalytic disk in lens case and leave the disk there until time to replace it. Add hydrogen peroxide, place lenses in the case, and leave for at least 6 hours.
- Never place neutralizing solution in a lens case with a catalytic disc. An unwanted chemical reaction may occur, or a gummy residue may form on the disc.
- Before inserting lenses in the eyes, make sure the hydrogen peroxide is completely neutralized by carefully following product instructions.

- Rinse lenses thoroughly with saline before inserting them.

Chemical Preservative Disinfection

- Store lenses for the prescribed period of time (usually a minimum of 4 hours) in a preservative disinfecting solution that is appropriate for the lens type.
- If you experience irritation, remove lenses and rinse them thoroughly with saline to remove any disinfecting solution.
- If not wearing lenses for prolonged periods after chemical disinfection, store the cleaned lenses in an appropriate multipurpose contact lens solution and change out the multipurpose solution in the storage container daily.

Combination Enzymatic Cleaning and Disinfection

- When combining enzymatic cleaning and disinfecting of the lenses as one step, select products compatible with your disinfecting system.
- Add appropriate solution (hydrogen peroxide or chemical disinfecting product) to the storage case of the disinfecting system.
- Place the lenses in the case and then add appropriate enzymatic cleaner.
- Follow directions for the appropriate disinfecting system listed previously.
- Rinse lenses thoroughly with saline to remove residual enzymes.

The second chemical disinfection method uses hydrogen peroxide as the antimicrobial agent. These products are good choices for patients with preservative allergies because they are preservative-free. Soft lenses are placed in purified hydrogen peroxide, and disinfection occurs with the liberation of oxygen from peroxide. Household hydrogen peroxide solution should not be used; its pH is too low, it is not sterile, and it may discolor lenses. After disinfection is completed, the peroxide is neutralized to trace levels by a neutralizing tablet that contains a delayed-release catalase or by the catalytic action of a platinum disc. This process takes approximately 6 hours.^{17,20}

One potential disadvantage of hydrogen peroxide disinfection is that patients may mistakenly insert the lens into the eye directly from the peroxide solution without neutralization. Patients must be warned not to perform a final rinse with the disinfecting solution before inserting their lenses, as they might do with a multipurpose chemical system. Emphasis on the neutralization step is

critical. A peroxide-soaked lens placed on the eye will likely cause a toxic keratitis, with manifestations of pain, photophobia, and redness. In this event, the patient should immediately remove the lens and flush the eye copiously with sterile saline solution or, if this is not available, even tap water. If signs and symptoms do not abate, prompt consultation with an eye care provider is warranted. Patients should be educated on appropriate replacement of the products and system components, such as the catalytic disc. An important point is that any sensation of discomfort or burning experienced by the patient when inserting contact lenses that have been disinfected with hydrogen peroxide is likely to mean incomplete neutralization, necessitating replacement of the disc. Hydrogen peroxide systems are not recommended for patients who wear lenses intermittently and leave their lenses in neutralized solution for extended days of storage. Patients with these wear habits should be advised to switch solutions after each peroxide cleaning to a multipurpose solution, or to change to daily disposable contact lenses. The hydrogen peroxide bottles also have a red cap to remind patients of the special handling required when in use.

Oxysept UltraCare is a catalase-based system. With this product, the user adds a delayed-release neutralizing tablet at the beginning of the 6-hour disinfecting cycle. Disinfection and neutralization then occur at the appropriate time intervals. This tablet contains catalase and cyanocobalamin; the latter ingredient turns the solution pink, reminding the user that the tablet has been added.²¹ The tablet is coated with hydroxypropyl methylcellulose, which helps lubricate the eye if the lens is not rinsed again between disinfection and insertion. It should not be used if crushed or cracked. A separate daily cleaning step is required. An enzymatic cleaner may be added weekly for protein removal.

When recommending a disinfecting method, the primary care provider should consider the patient's ability or reliability in adherence to the lens care regimen, wearing schedule, and convenience. Peroxide-based systems provide excellent disinfection against many organisms and essentially eliminate solution sensitivity issues. They are not well suited, however, for intermittent wear of disposable lenses or to adoption by the careless user, who may inadvertently instill peroxide in the eye. If the patient has a history of sensitivity reactions to lens solutions or is unsure whether sensitivity exists, it is best to recommend a product containing one of the nonsensitizing preservatives.

Multipurpose Products

Initially, manufacturers recommended three separate products for cleaning, removal of protein deposits, and disinfection in care regimens for soft contact lenses. More recently, a trend toward use of multipurpose solutions for all of these functions has emerged, in attempt to simplify lens care and improve adherence to optimal wear regimens. The original sequence for cleaning and disinfecting contact lenses was to rub, rinse, and soak the lens overnight. However, with promotion of the “no-rub” technique by manufacturers of multipurpose solutions, patients often are confused about proper lens care.^{22,23} Several studies have demonstrated that with multipurpose solutions, a no-rub technique does not adequately remove protein and other deposits and cosmetics compared with active rubbing of the lens with the fingertip. To reduce risk of infection, irritation, and other complications, proper rub, rinse, and soak technique should be recommended with use of all multipurpose solutions. This recommendation is shared by FDA, the American Optometric Association, and the American Academy of Ophthalmology.²⁴

The newest multipurpose solutions were made with due consideration of both disinfection and comfort and feature two significant chemical preservatives and agents to improve wettability. Biotrue contains a lubricant naturally found in the eye (hyaluronan), while matching the pH of healthy tears to improve the efficacy of the disinfectants.²⁵ OptiFree PureMoist features the HydraGlyde Moisture Matrix, which creates a moisture barrier on the surface of the lens and helps prevent protein and dirt buildup and aid in comfort. Blink RevitaLens solution is the only agent that contains the preservative alexidine, which provides broad antimicrobial coverage and often is found in mouthwashes.^{26,27} **Table 29–5** compares products made specifically for use with soft contact lenses.

TABLE 29–5 Selected Products for Use With Soft Lenses

Trade Name	Disinfectant(s)/Preservative(s)
Daily Cleaner	
Sensitive Eyes Daily Cleaner	Sorbic acid 0.25%, EDTA 0.5%
Preservative-Free Daily Cleaners	
Sof/Pro 2 Sterile Extra Strength Daily	n/a

Trade Name	Disinfectant(s)/Preservative(s)
Cleaner	
Sereine Extra Strength Daily Cleaner	n/a
Combination Hydrogen Peroxide Disinfecting Solutions and Rinsing/Neutralizing Products	
Clear Care	Hydrogen peroxide 3%
Clear Care Plus	Hydrogen peroxide 3%
Oxysept UltraCare	Hydrogen peroxide 3%
Refine One-Step	Hydrogen peroxide 3%
Enzymatic Cleaner	
Ultrazyme Enzymatic Cleaner	n/a
Preserved Saline Solutions	
Sensitive Eyes Plus Saline	Sorbic acid 0.1%, EDTA
Clear Care Rinse & Go	Polyquaternium 0.001%
Good Sense Saline Solution	Sorbic acid 0.1%, EDTA
Preservative-Free Saline Products	
PuriLens Plus ^a	n/a
LacriPure	n/a
Simply Saline	n/a
Rewetting/Lubricating Solutions	
Blink Contacts	Stabilized oxychloro complex 0.005% (OcuPure)
TheraTears Contact Lens Comfort Drops	Sodium perborate
Opti-Free Puremoist Rewetting Drops	Polyquaternium 0.001%, EDTA 0.05%
Opti-Free Express Rewetting Drops	Polyquaternium-1 0.001%,
Opti-Free Replenish Rewetting Drops	Polyquaternium-1 0.001%

Trade Name	Disinfectant(s)/Preservative(s)
Renu Rewetting Drops	Sorbic acid 0.15%, EDTA 0.1%
Renu MultiPlus Lubricating and Rewetting Drops	Sorbic acid 0.1%, EDTA 0.1%
Sensitive Eyes Rewetting Drops	Sorbic acid 0.1%, EDTA 0.025%
Multipurpose Solutions	
Biotrue	Polyaminopropyl biguanide (PHMB) 0.00013%, polyquaternium 0.0001%, EDTA
Complete Multi-Purpose Solution Easy Rub Formula	Polyhexamethylene biguanide 0.0001%, EDTA
OPTI-FREE Express	Polyquaternium-1 0.001%, myristamidopropyl dimethylamine 0.0005%, EDTA
OPTI-FREE PureMoist	Polyquaternium-1 0.001%, myristamidopropyl dimethylamine 0.0006%, EDTA
OPTI-FREE Replenish	Polyquaternium-1 0.001%, myristamidopropyl dimethylamine 0.0005%
Renu Fresh	Polyaminopropyl biguanide 0.0001%, EDTA
Renu Sensitive	Polyaminopropyl biguanide 0.00005%, EDTA
Blink RevitaLens	Alexidine dihydrochloride 0.00016%
	Polyquaternium-1 0.0003%, EDTA

^a To be used only with the PuriLens UV System.

Key: EDTA = Ethylenediaminetetraacetic acid; n/a = not applicable.

Reactions to solutions should always be considered in attempts to discern the cause of patient symptoms or findings of surface irritation during an eye examination. Most if not all of the chemicals listed as preservatives can cause irritation to the epithelium.²⁸ If signs and symptoms are related to solution use, a possible remedy is to use a final saline rinse before lens insertion or to

change to another formulation of multipurpose solution that uses a different preservative. Another alternative for patients who are sensitive to chemical-based care systems is the PuriLens system, as discussed earlier.

Cleaning Products

Daily use of separate cleaners and protein removal products, in addition to use of multipurpose solutions, generally is not necessary with disposable lenses that will be discarded after a few weeks of wear. These products should be recommended if patients have longer replacement schedules (>1 month) or demonstrate rapid formation of heavy deposits on lenses.²⁹ The nature of deposits varies, but they generally consist of proteins and lipids from lacrimal secretions. Environmental factors also can create deposits, such as tar and nicotine from tobacco products, pet dander, and dust.

Soft lens cleaning solutions generally contain a nonionic detergent, a wetting agent, a chelating agent, buffers, preservatives, and, in some cases, polymeric cleaning beads.²⁵ Cleaning with a surface-active cleaner can be done daily or, in the case of continuous-wear lenses, each time they are removed from the eyes. These products should be shaken before use. Care should be taken to ensure that no residue from the cleaning solution remains on the lens before insertion. Some surface-active cleaners (e.g., Bausch + Lomb Sensitive Eyes Daily Cleaner) have a lower viscosity, and such products may be a good choice for patients who have difficulty completely rinsing the cleaner off their lenses.

Although the surface-active cleaners generally are quite effective in removing lipid deposits, they remove tenacious protein debris less successfully. Enzymatic cleaners constitute an additional cleaning aid that can solve this problem.²⁹ The component enzymes hydrolyze polypeptide bonds of protein and dissolve the protein deposits. For the enzyme solution to work properly, however, the lens must be cleaned with a surface-active cleaner first; enzymes are ineffective on debris that covers or is mixed with protein.

An enzymatic cleaner is recommended in accordance with the disinfection system used by the patient. Ultrazyme contains the active ingredient subtilisin A and is used weekly with hydrogen peroxide cleaning systems. This product can be placed in the peroxide solution, thereby cleaning and disinfecting lenses at the same time.

Saline Solutions

A common source of confusion among patients is the use of saline solutions in lieu of disinfecting agents. At one point in the evolution of lens care, isotonic normal saline was the basic solution used for rinsing, thermally disinfecting, and storing soft contact lenses.^{25,29} It is now recognized, however, that saline used alone lacks disinfecting properties, and the health care provider should direct the patient toward a suitable multipurpose or hydrogen peroxide solution.

Saline still has a use as a final rinsing agent before insertion, especially for patients who experience eye irritation from the chemicals in multipurpose solutions. Prepared saline is available in either preserved or preservative-free forms. If preservative-free, the saline solutions can be used within a 30-day time period if they are in a multiuse bottle. Patients using nonpreserved saline should be counseled that only aerosolized solutions can be used to rinse lenses just before insertion into the eye. Other forms of saline, such as intravenous normal saline or saline nasal sprays, are not suitable for rinsing because these products usually are too acidic for use with soft contact lenses. Patients should not try to make their own saline solution, however, because it can become easily contaminated and cause infections.

Rewetting Solutions

Because dryness and discomfort with contact lens wear are common, additional lubricating or wetting drops are often recommended for use during lens wear. Exposure of lenses to wind and high temperature also causes some dehydration, even with the lens in the eye. Thus, encouraging patients to wear sunglasses to minimize exposure is beneficial to prevent these issues.

However, if dryness and discomfort occur, these accessory solutions permit lubricating and rewetting and, in some cases, cleaning of the soft lens while on the eye. Patients should be directed toward products for specific use with contact lenses, and to avoid drops preserved with benzalkonium chloride, which can cause irritation, discoloration of lenses, punctate keratopathy, and/or toxic ulcerative keratopathy.³⁰ Preservative-free lubricating drops also are a good alternative. The associated discomfort is sometimes relieved by instilling 1–2 drops of rewetting solution. To minimize risk of contamination, the tip of the applicator bottle should not touch the eye, eyelid, or any other surface.

Generic Solutions

Many generic versions of brand-name solutions are now available. However, patients who choose to buy generic (e.g., mass merchandiser–labeled) multipurpose lens solutions may be purchasing older, potentially obsolete formulas. Mass merchandisers generally acquire older formulations of nationally known brands of multipurpose solutions and then market them under their private label. In addition, the composition of a particular generic formulation can vary because the generic brand stores submit bids to manufacturers two or three times per year. Generally, patients should not use generic brands unless they carefully read the label and compare all ingredients with those of the product recommended by their eye care or other provider. Manufacturers are not required to use the same name for generic and brand-name ingredients, so comparing formulations may be difficult.³¹

Product Incompatibility

Several incompatibilities may be incurred during mixing of soft lens products. Most manufacturers test for compatibility within their own product lines; however, compatibility with other manufacturers' products usually is not determined. Generally, chemical disinfecting solutions should not be used interchangeably or concurrently, as discussed earlier.

Insertion and Removal

Table 29–6 provides instructions for inserting and removing soft lenses.

TABLE 29–6 Insertion and Removal of Soft Lenses

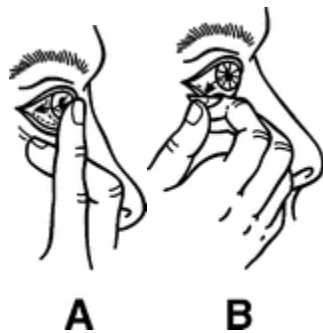
Insertion

- Wash your hands with noncosmetic soap and rinse thoroughly; dry hands with a lint-free towel.
- Remove one lens from its storage container.
- Rinse the lens with saline solution to dilute any preservatives left from disinfection (optional).
- Place the lens on the top of a finger, and examine it to be sure it is not inside out. This determination can be made by means of the “taco test”: Gently fold the lens at the apex (not the edges) between your thumb and forefinger. The edges should look like a taco shell with the edges pointed inward. If the edges roll out, the lens is inverted and must be reversed.

- Examine the lens for cleanliness. If necessary, clean it and rinse again.
- Place the lens on the eye using the procedure described for GP lenses (Table 29–9).
- Repeat all steps with the other lens.

Removal

- Before removing the lenses, wash hands with a noncosmetic soap; rinse hands thoroughly and dry them with a lint-free towel.
- Using the middle finger, pull down the lower lid of the right eye. Touch the index finger to the lens and slide the lens off the cornea, as shown in drawing A.
- Using the index finger and thumb, grasp the lens and remove it (drawing B).
- Repeat the procedure for the left eye.



Gas-Permeable Contact Lens Care

The care of GP contact lenses follows the same general guidelines as for soft lenses, but the solutions for GP and soft lenses are not interchangeable. The patient's eye care provider will recommend various products and regimens for the particular GP lens type, and lens wearers should be advised against substituting other products for those specifically recommended.

Rigid lens care involves the steps of cleaning, disinfecting, soaking, and wetting (Figure 29–2), which should be performed each time the lenses are removed from the eye, for optimal lens care.³² Modern solutions combine these steps in various formulations. Because GP lenses are replaced less frequently, allowing more time for deposits to accumulate, separate solutions for daily cleaning and protein removal are still popular. Oxidation systems (hydrogen peroxide) also can be used, but heat disinfection should not be used with GP lenses. Rinsing with tap water also is not recommended because of microorganisms in the water. Tables 29–2, 29–4, and 29–7 specify proper cleaning and disinfecting procedures for rigid contact lenses.

FIGURE 29–2 Basic care regimen for rigid contact lenses.

TABLE 29–7 Specific Cleaning Procedures for Gas-Permeable (GP) Lenses	
• Use the cleansing, soaking, and storage products recommended by your eye care provider for care of your lenses. • If you are unsure of your lens type, ask the eye care provider about proper cleaning procedures. • Upon removal of the lens, apply an appropriate cleaning solution to both lens surfaces. Then rub the lens with the tip of the forefinger against the palm of the opposite hand, using a back-and-forth motion, to avoid chipping an edge, which may occur if the lens is cleaned between the forefinger and the thumb. Do not apply too much pressure. If debris is still on the lens, soak a cotton swab in the surfactant cleaner, and use the swab to clean the lens. • Soak and store the lenses in a soaking or storage solution recommended by the eye care provider for the specified amount of time. Rewet lenses before inserting them in the eyes. • Enzymatic cleaning also may be recommended by your eye care provider and typically is performed weekly.	

Source: Reference 31.

Product Selection Guidelines

With the abundance of combination wetting–disinfection solutions now on the market, the appropriate lens care regimen for GP lenses is fairly straightforward. Patients who wear GP lenses should be advised to purchase a surface-active cleaning product, an enzymatic product, and a conditioning or storage solution, depending on the type of lens worn.²⁵ A rewetting or reconditioning product also should be recommended. Table 29–8 lists examples of products for use with GP lenses.

TABLE 29–8 Selected Products for Use With Gas-Permeable Lenses								
TABLE 29–8 Selected Products for Use With Gas-Permeable Lenses								
Manufacturer	Product	Wetting	Daily	Weekly	Function(s)	Cleaning/	Wetting/	Lubrication
Manufacturer	Product	Wetting	Cleaner	Cleaner	Soaking	Soaking/	Soaking/	Lubrication
			Cleaner	Cleaner	Soaking	Soaking	Soaking	Lubrication
Alcon	Clear Care					X		
Alcon	Clear Care					X		

		Function(s)						
Manufacturer	Product	Wetting	Daily Cleaner	Weekly Cleaner	Soaking	Cleaning/ Soaking	Wetting/ Soaking	Lubrication
	Clear Care Plus				X	X	X	
Bausch + Lomb	Boston Advance Comfort Formula Conditioning Solution						X	
	Boston Advance Cleaner		X					
	Boston Original Formula Conditioning Solution		X		X		X	
	Boston Simplus Multi-Action Solution	X	X		X	X	X	
	Boston One Step Liquid Enzymatic Cleaner			X				
	Boston Rewetting Drops	X						
Contex	Clear Clean		X			X	X	
	Polish Brite			X				
Johnson & Johnson Surgical Vision, Inc	Blink Contacts							
Lobob	Optimum		X					

Manufacturer	Product	Function(s)						
		Wetting	Daily Cleaner	Weekly Cleaner	Soaking	Cleaning/ Soaking	Wetting/ Soaking	Lubrication
Lobob	Optimum Strength Cleaner		X					
	Optimum Wetting	X						
	Optimum Rewetting	X						
	Optimum Cleaning, Disinfecting, Storing, Storage		X X			X X		
Menicon	Unique pH	X	X		X	X	X	
Menicon	Unique pH	X	X		X	X	X	
	Progent Protein Remover		X X					
	Sereine Solution							
Optikem	Operational					X X		
Optikem International	Operational					X X		
	Solution							

Key: EDTA = Ethylenediaminetetraacetic acid; n/a = not applicable.

Key: EDTA = Ethylenediaminetetraacetic acid; n/a = not applicable.

Source: Adapted with permission from White P. 2019 *Contact Lenses and Solutions*

Summary: July 2019 supplement to *Contact Lens Spectrum*, Pentavision LLC. Available at: https://www.clspectrum.com/resources/class-pdfs/7_19-class_final. Accessed April 15, 2020.

Cleaning Solutions

Cleaning solutions are used more often for GP lenses because of the longer wear time before disposal. Accumulated residue, primarily proteinaceous debris and lipids from tears and glandular secretions, acts as a growth medium for bacteria. If not routinely removed by daily cleaning, the residue

may harden to form coatings or tenacious deposits that decrease visual acuity and cause cloudiness of the lens. Cleaners contain silica gel, which acts to mechanically break the adhesive bonds that have formed between the lens and the deposits.

Storage Solutions

Storage solutions, also known as conditioning solutions, are used to store rigid contact lenses after removal. The stored lenses are maintained in a constant state of hydration for maximum comfort and visual acuity, and the conditioning agent also aids in removing deposits that accumulate on the lenses during wear. These solutions also increase comfort by providing cushioning and lubrication when the contact is reinserted into the eye.

Rewetting Solutions

Rewetting solutions are intended to clean and rewet the contact lens while it is in the eye. These solutions depend on the use of surfactants to loosen deposits; removal is assisted by the natural cleaning action of blinking. Although these products function well to recondition the lens, the cornea benefits more if the lens is actually removed, cleaned, and rewetted. Removing the lens for even a brief time allows the cornea to be resurfaced with a new proteinaceous or mucinaceous layer.

To maintain sterility in rewetting products, preservative levels are carefully selected in their formulation. Higher levels do not necessarily result in increased effectiveness and may lead to impaired wetting or corneal irritation because of the adsorption of preservatives onto the lens. Most rewetting agents are preserved, multidose products. Lens wearers who use these products frequently should be encouraged to use products that contain preservatives such as oxychloro complex or perborates. An important point to emphasize in patient counseling is that preserved artificial tears and rewetting agents are different; most preserved artificial tears are incompatible with contact lenses.³³

Enzymatic Solutions

As the silicone content of GP lenses increases, so does the amount of protein adherence. Silicone acrylate lenses have an active surface that promotes the binding of tear constituents. Protein deposits on a lens will decrease its oxygen

permeability and may contribute to wear discomfort. If daily cleaning is not sufficient, lenses of this type should be cleaned with an enzymatic product once weekly.³² Omission of this cleaning step may result in the need for professional polishing or replacement of the lens.

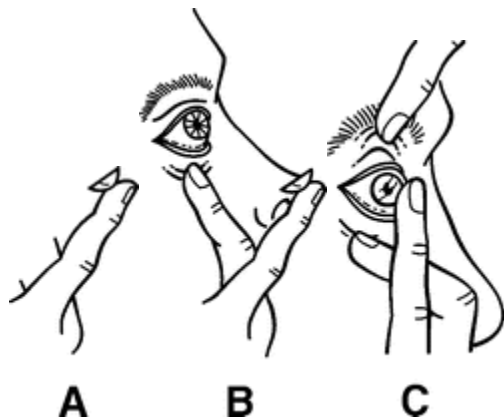
Insertion and Removal

Wearers of GP lenses should be counseled to follow proper insertion and removal procedures ([Table 29–9](#)).

TABLE 29–9 Insertion and Removal of Gas-Permeable Lenses

Insertion

- Wash your hands with noncosmetic soap and rinse thoroughly; dry hands with a lint-free towel.
- Remove one lens from its storage container.
- Rinse the lens with fresh storage or soaking solution, and inspect it for cleanliness and signs of damage (cracks or chips).
- If a wetting/storage solution is being used, place a few drops on the lens.
- Place the lens on the top of the index finger, as shown in drawing A.
- Place the middle finger of the same hand on the lower lid and pull it down (drawing B).
- With the other hand, use a finger to lift the upper lid, and then place the lens on the eye (drawing C).
- Release the lids and blink.
- Check vision immediately to see if the lens is in the proper position.
- If vision is blurred, blink three or four times. If vision is still blurred, the lens may be off center, on the wrong eye, or dirty.
 - Instill 1–3 drops of rewetting or reconditioning drops into the eye.
 - If vision is not improved, remove the lens, place several drops of wetting or storage solution onto both surfaces, and reinsert lens.
- Repeat all steps with the other lens.

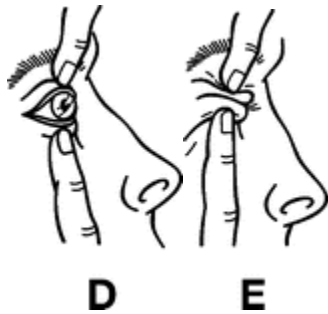


Removal

- Before removing the lenses, wash hands with a noncosmetic soap; rinse hands thoroughly and dry them with a lint-free towel.
- Fill the storage cases with soaking or storage solution.
- Remove the top from the cleaning solution.
- Place a hand (or a towel) under the eye.
- Use one of the following methods to remove the lens from the eye.

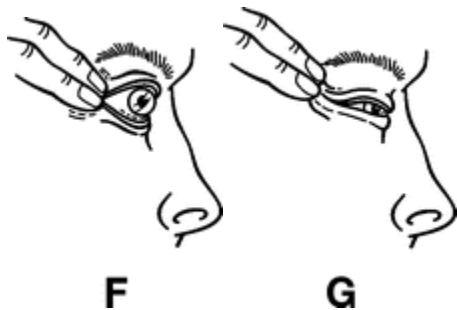
Two-Finger Method of Removing Lenses

- Place the tip of the forefinger of one hand on the middle of the upper eyelid by the lashes, as shown in drawing D.
- Place the forefinger of the other hand on the center of the lower lid margin (drawing D).
- Push the lids inward and then together, as shown in drawing E. The lens should pop out.
- If the lens becomes displaced onto only the white part of the eye, recenter the lens and try again.



Temporal Pull/Blink Method of Removing Lenses

- Place an index finger on the temporal edge of the lower and upper lids. Initially, widen the eyelids a little (drawing F).
- Stretch the skin outward and slightly upward without allowing the lid to slide over the lens. Blink briskly, as shown in drawing G. The lens will pop out because of the pressure of the eyelids at the top and bottom of the lens. Blinking facilitates removal after the lids have been tightened around the lens.



Lens Storage Case

Patient education on the care of all contact lenses must include discussion of the proper care and cleaning of the contact lens storage case as well as the lens material. A dirty lens case can become contaminated with a biofilm that will attract pathogens, thereby increasing the risk of infection. The lens case should be cleaned daily. After lens insertion, the case (and case lid, if separate) must be emptied, rinsed with the same disinfecting solution, wiped, and air-dried between uses.³⁴ Tap water should not be used. All added solutions should be discarded daily. The case should not be used if cracked and should be replaced periodically, at least every 3 months.^{32,34}

Follow-up Care

Follow-up care is essential for the long-term success of contact lens wear. The minimum recommendation is 1 year between provider visits in the case of uncomplicated lens wear. These visits allow the prescriber to evaluate the integrity of the lenses worn and the condition of the cornea. Patient education content on the wearing schedule, replacement frequency, and lens care regimen also should be reviewed. Regular contact lens follow-up care is an important aspect of prevention of contact lens complications.

Contact Lens–Related Problems

Both soft and GP contact lenses provide good vision and safe, comfortable wear over years of use, provided that they are fitted properly and patients adhere to correct care regimens. Unfortunately, complications of contact lens wear have not been eradicated despite advances in material, lens design, and solutions. In general, soft contact lens wearers tend to have more complications because less tear exchange occurs beneath the lens and because wear times are longer, including overnight. Problems with GP lenses tend to be related to improper fit. Although occasional slight redness and mild discomfort are common with contact lens wear, health care providers likely to encounter patients with ocular complaints should be familiar with more severe symptoms that may herald significant complications, including threats to

vision. Whenever a patient presents with signs or symptoms that are believed to be related to contact lens wear, discontinuing lens wear is recommended until the underlying cause is diagnosed and treated. Therefore, every contact lens wearer should have eyeglasses available as a backup.

Evaluation of a contact lens–related complaint should begin with a thorough history of the problem. During the patient interview, the health care provider should determine what types of ocular signs and symptoms are present and for how long. Ascertaining whether the patient has a previous history of eye problems and identifying current medications will give a general sense of the etiology and urgency of the presenting problem. This information also will help to determine whether the problem is related to noncompliance with care regimens or to drug–lens interactions. Determining which type of contact lenses a patient is wearing and how long the patient has worn them is crucial in assessing problems that are related to improper lens care or deteriorated lenses. Patients should be asked to describe how they care for their lenses, which lens care products they use, and whether they have recently changed products.

Unfortunately, mild and severe complications of lens wear manifest with similar symptoms that overlap and vary in degree. For example, mild redness and irritation in both eyes occurring at the end of the day for several weeks or months are likely to reflect dryness that might resolve with a change in lens material, wearing schedule, or lubricating drops. However, a clinical presentation consisting of acute symptoms of marked, sectoral redness in one eye, accompanied by photophobia and pain that started 1 day earlier, suggests a more severe problem such as a corneal ulcer. This situation warrants immediate medical attention and should lead to referral to an urgent care center or a hospital emergency department.

The following signs and symptoms are common manifestations of lens-related problems:

- *Itching.* Patients usually are not allergic to lens materials, but they may have an allergy to solutions. Itching may also be a sign of allergic conjunctivitis unrelated to lens wear.
- *Blurred vision.* Mild blurring may suggest wrong lens power, accidental switching of lenses between eyes, an inside-out lens on the eye, or debris buildup on the lens. Blurring also accompanies problems with the ocular surface, such as superficial keratitis, corneal abrasion, and

corneal edema associated with infiltration or ulceration.

- *Redness.* Redness can occur as a response to any of numerous insults. The degree of redness typically, but not always, corresponds to the severity of the problem. Mild, diffuse redness can accompany end-of-day dryness, whereas severe redness, especially sectoral, can indicate a corneal problem. Ocular decongestants reduce the mild conjunctival hyperemia associated with prolonged lens wear. On cessation of use of these topical agents, however, a rebound hyperemia can result, especially with use for longer than 72 hours. Therefore, routine use of these products should be avoided, and if symptoms persist, the patient should be referred to an eye care provider.
- *Pain.* Pain is a significant finding because it is likely to be related to a pathologic process involving the eye's corneal nerve endings. Mild discomfort or irritation is not uncommon among wearers of all types of contact lenses. It may be related to the material, lens fit, or a torn or dirty lens. Severe pain or deep aching of the eye can signify corneal abrasions, infiltrates, or ulcers; if so, the pain typically persists even after removal of the lens. These latter symptoms are likely to represent urgent, sight-threatening conditions, and referral to an eye care provider is essential.
- *Fogging.* Misty or smoky vision can be caused by coatings or deposits on lens surfaces or by poor wetting of the lens while on the eye.
- *Photophobia (light sensitivity).* Similar to pain, photophobia suggests complications with the cornea or may be a symptom of iritis. This symptom necessitates referral to an eye care provider.
- *Excessive tearing.* Corneal nerves can start a feedback loop that promotes tearing; therefore, irritation to the corneal surface, such as a torn or dirty lens, will increase tearing.
- *Flare.* Point sources of light that have a sunburst or streaming quality can be caused by inadequate optic zone size or decentration of a poorly fitting lens.
- *Lens falling out of the eye.* Improper fit is usually the cause; however, even properly fitted rigid lenses may occasionally slide off the cornea or be blinked out of the eye. Soft lenses that dry out on the eye may move excessively and dislocate.
- *Squinting.* This reflexive maneuver is the result of excessive movement of a lens or a poorly fitted lens. The wearer will squint as an unconscious stratagem to center the optical portion of the lens over the pupil. Squinting also may indicate improper lens power.

Redness, discomfort, and dryness are the most common ocular complaints and the leading causes for discontinuing lens wear. Even with brand new contact lenses, mere presence of the lens disrupts the tear film and alters the environment of the anterior ocular surface, with corresponding clinical effects. A change in lens material or solution, alteration of lens fit, or use of lubricating drops usually leads to symptomatic improvement.

By contrast, microbial keratitis (leading to corneal ulceration) is the most serious complication of contact lens wear. The health care provider should be alert for signs and symptoms of this condition including blurred vision, redness, pain, light sensitivity, and watering that often worsen even after discontinuation of lens wear. A white infiltrate visible on the cornea necessitates urgent referral for evaluation by an eye care provider. Removal of contact lenses and prompt treatment are crucial to improve outcomes.

Overall, distinguishing common lens wear–associated complaints from signs of more severe inflammatory or infectious complications can be challenging. Considerations include whether one or both eyes are involved, the duration and severity of symptoms, and whether symptoms are isolated or found in conjunction with others. Even experienced health care providers have difficulty distinguishing inflammatory from infectious complications. Timely referral to an eye care provider is indicated if the clinical findings suggest more than lens wear–associated symptoms. [Chapter 28, Ophthalmic Disorders](#), addresses other problems that can be mistaken for contact lens issues.

Precautions for Contact Lens Wear

Adverse Effects of Drugs

Many undesired effects have been reported when a patient who wears contact lenses ingests, applies, or otherwise encounters certain drugs ([Table 29–10](#)). Wearers of soft hydrophilic contact lenses should be particularly cautious about exposure of the lenses to chemicals. Such chemicals, many of which penetrate and bind with the lens material, can come from cosmetics, environmental pollutants, and ophthalmic and systemic products. The health care provider must be fully cognizant of these potential drug-induced problems to counsel patients effectively.

TABLE 29–10 Drug–Contact Lens Interactions**Changes in Tear Film or Production*****Decreased Tear Volume***

Alcohol

Anticholinergic agents

Antihistamines

Antipsychotics

Beta blockers

Benzodiazepines

Botulinum toxin type A (Botox)

Conjugated estrogens

Diuretics/thiazides

Histamine type 2 (H₂) receptor antagonists

Oral contraceptives

Pain relievers—ibuprofen, acetaminophen-containing products

Phenothiazines

Proton pump inhibitors

Retinoids

Selective serotonin reuptake inhibitors

Sildenafil citrate

Statins

Timolol (topical)

Tricyclic antidepressants

Vardenafil HCl

Increased Tear Volume

Cholinergic agents
Garlic (dietary supplement)
Reserpine
Changes in Lens Color (Primarily With Soft Lenses)
Diagnostic dyes (e.g., fluorescein)
Epinephrine (topical)
Fluorescein (topical)
Nicotine
Nitrofurantoin
Phenazopyridine
Phenolphthalein
Phenothiazines
Phenylephrine
Rifampin
Sulfasalazine
Tetracycline
Tetrahydrozoline (topical)
Changes in Tear Tonicity
Pilocarpine (8%)
Sodium sulfacetamide (10%)
Lid/Corneal Edema
Chlorthalidone
Clomiphene
Conjugated estrogens
Oral contraceptives

Primidone
Ocular Inflammation/Irritation
Diclofenac (topical ophthalmic)
Garlic (dietary supplement)
Gold salts
Isotretinoin
Salicylates
Changes in Refractivity (Induction of Myopia)
Acetazolamide
Sulfadiazine
Sulfamethizole
Sulfamethoxazole
Sulfisoxazole
Changes in Pupil Size
<i>Pupillary Dilation</i>
Anticholinergic agents
Antidepressants
Antihistamines
CNS stimulants
Kava
Phenothiazines
<i>Pupillary Miosis</i>
Opiates
Miscellaneous Drug Effects
Digoxin—increased glare

Sedative-hypnotics/muscle relaxants—decreased blink rate
Ribavirin—cloudy lenses
Topical ciprofloxacin/prednisolone acetate—precipitate

Key: CNS = Central nervous system.

Source: Adapted with permission from Engle JP. Contact lens care. *Am Druggist*. 1990;201:5465. Updated with information from references [35](#) and [38](#).

Topical Medications

In general, patients should be warned not to use any ophthalmic solution, suspension, gel, or ointment in the eye when contact lenses are in place. A nonprescription ophthalmic product that is not specifically designed for compatibility with contact lenses also should not be used when lenses are in the eye. Soft lenses can absorb chemical compounds from topically administered ophthalmic products.³⁵ Topical administration of ophthalmic drugs also may have physiologic consequences or may modify pharmacologic responses to drugs. The use of solutions that may be considered benign, such as artificial tears, may reduce tear breakup time and alter the distribution of the mucoid, aqueous, and lipid components of tears, potentially causing initial discomfort on instillation of the drops. A topical drug administered while soft lenses are in place may have an exaggerated pharmacologic effect. The soft lens may absorb the drug and either release it over time, creating a sustained-release dosage form, or bind it tightly so that none of it is released into the eye. Furthermore, the presence of any kind of contact lens may increase the amount of time the medication is in contact with the eye. Finally, increased drug absorption may occur secondary to a compromised corneal epithelium from contact lens wear. The only exceptions to this rule are products specifically formulated to be used with contact lenses, such as rewetting drops, or those products that an eye care provider has specifically recommended for use with contact lenses.

After a drug solution has been instilled into the eye, insertion of a lens must wait until the solution has cleared from the lower eyelid's precorneal (conjunctival) pocket (approximately 5 minutes). Ideally, when topical ophthalmic ointments, gels, or suspensions are being used, the lenses should

not be worn at all.

Airborne Drugs and Particulate Matter

Some drugs that are present in indoor air may damage lenses, so caution is warranted in prescribing medications that are administered by inhalation for contact lens wearers. Similarly, lens wearers who have been exposed to a large amount of cigarette smoke have discovered a brown discoloration and nicotine deposits on their lenses. Other particulate matter, such as spray chemicals, smoke from grills, spattered cooking oil, pollen, animal dander, sawdust, or sand, also may create issues for contact lens wearers.

Systemic Medications

Use of a systemic medication often has far-reaching and unanticipated adverse effects aside from the expected pharmacodynamic actions. Perhaps the most common eye-related manifestation of such toxicity is the ocular discomfort or irritation and lens intolerance experienced by contact lens wearers taking certain systemic drugs. These patients often present with complaints of new-onset eye dryness or irritation and intolerance to previously well-established contact lens wear and request a nonprescription product to provide symptomatic relief. Although such symptoms are similar to those arising with other, more common underlying problems, such as improper contact lens hygiene, health care providers should always consider the pharmacology of specific systemic medications as well as potential relationships between medication initiation and onset of symptoms.³⁵

The effects of medications on the eye vary by drug class. As a general rule, compounds with anticholinergic effects can reduce tear volume and induce dry eye, with or without concomitant loss of accommodation and blurry vision.³⁶ Other classes of drugs, such as hormones (most notably birth control pills), also may alter tear volume and the contour of the corneal surface, resulting in blurring and contact lens intolerance. Some systemic medications are secreted into tears and may interact with the component material of the (primarily soft) lens. For example, rifampin will stain both lenses and tears orange. Drugs and dietary supplements such as gold salts and garlic are secreted into the tears, with consequent ocular irritation. Other drugs may affect tear production, the refractive properties of the eye, the shape of the cornea, or the actual lens ([Table 29–10](#)). Some medications may influence the

size of the pupil, leading to complaints of glare or flare when lenses are in place. Visual performance may be diminished, especially in patients who wear multifocal lenses or GP lenses, for which pupil size may determine placement of the reading segment or the optic zone of the lens, respectively.^{37,38}

Use of Cosmetics

Contact lens wearers should choose—and use—cosmetics with care. The patient should insert lenses before applying makeup and avoid touching the lens with eyeliner or mascara applicators. Cosmetics, moisturizers, and makeup removers with an aqueous base should be used, because oil-based products may cause blurred vision and irritation if they are deposited on the lens. Water-based products are always preferable, and when possible, users should choose makeup that has been specifically formulated for contact lens wearers. Lens wearers should avoid loose powders (e.g., face, eye) and instead use pressed or cream-based products, if available. Water-resistant mascara (as opposed to waterproof mascara, which requires an oil-based remover) should be applied only to the very tips of the lashes. Eyeliners should never be applied inside the eyelid margin; the liner material can clog glands in the eyelid and contaminate the contact lens. Eye makeup products should be discarded and replaced at least every 3 months.³⁹

Aerosol products, such as hair spray, body sprays, perfumes, sunscreens, and insect repellants, must be used with caution: Users should close the eyes when applying the product and step out of the mist before opening the eyes. Nail polish, hand creams, and perfumes also should be applied only after the lenses have been inserted. Men often contaminate their lenses with hair preparations and spray deodorants. Lens wearers should be reminded to take special care to clean the hands thoroughly before handling their lenses. Soaps that contain cold cream or deodorants should be avoided.

Exclusions for Self-Care

When the lens care regimen is appropriate but the lenses are old or, in the case of rigid lenses, chipped or scratched, the patient should see an eye care provider for replacement lenses. Other clinical scenarios that necessitate referral are those involving suspected vision changes, onset of deep aching of the eyes, overdue regular eye examination by more than 1 year, and suspected interaction between the lenses and systemic medications. Patients

experiencing lens problems related to any of the medical conditions or other factors discussed in the section “Contraindications and Warnings for Contact Lens Wear” also should be referred for further evaluation.

Cases 29–1 and 29–2 illustrate the assessment of two different patients with contact lens–related problems.

Case 29–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient’s symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient is a contact lens wearer who complains of a “fogginess” in both eyes that is not present when she wears her glasses, as well as dry, itchy eyes. She has experienced these symptoms for the past week, but she states that they also typically occur toward the end of each month. She wears monthly disposable soft contact lenses. She reports changing her lenses on the first of each month and does not sleep in them. The patient’s lens care regimen includes soaking the lenses daily in fresh solution using the same multipurpose solution. She does not discard the solution at the end of the 90-day usability period. She also does not rub or rinse the contact lenses daily.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient’s symptom(s)	Patient reports that she experiences less itching and redness when she first starts wearing a new pair of contact lenses and when she starts using a new bottle of solution.
c. Description of	Patient has not tried any measures to relieve her symptoms.

Relevant Evaluation Criteria	Scenario/Model Outcome
the patient's efforts to relieve the symptoms	
d. Patient's identity	Kate Smith
e. Patient's age, gender, height, and weight	30 years, female, 5 ft 6 in., 120 lb
f. Patient's occupation	Accountant
g. Patient's dietary habits	N/A
h. Patient's sleep habits	The patient gets about 7 hours of sleep per night.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	None
j. Allergies	NKA
k. History of other adverse reactions to medications	None
l. Other (describe) -----	Ms. Smith is a nonsmoker who reports social alcohol use on the weekends.
She uses oil-based cosmetics.	
Assess	
2. Differentiate	Discomfort due to poor contact lens hygiene and care, as well as

Relevant Evaluation Criteria	Scenario/Model Outcome
patient's signs/symptoms, and correctly identify the patient's primary problem(s).	premature contact lens wear due to inadequate care, but the problem also could be due to oil-based cosmetic use.
3. Identify exclusions for self-treatment.	In view of the absence of any concurrent medical conditions or concomitant medications, Ms. Smith is a good candidate for self-care.
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer the patient to an eye care provider. (2) Recommend self-treatment. (3) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Recommend using proper contact lens care and hygiene and switching to water-based cosmetics.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Your symptoms suggest that you are not using an appropriate care regimen for your contacts. Not rinsing or rubbing your lenses daily can allow buildup of proteins on the lens, leading to fogginess. Also, wearing oil-based cosmetic products can lead to fogginess as well."
7. Explain to the	"Fogginess is a common contact lens complaint. Your symptoms are

Relevant Evaluation Criteria	Scenario/Model Outcome
patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	present only toward the end of a month of lens wear, when appropriate contact lens care has not been used, and may be exacerbated by your use of oil-based cosmetics. This is likely to be a self-care issue and does not require that you see an eye care provider at this time.”
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
a. Appropriate dose and frequency of administration	“Discard the previous day’s solution and use new contact lens multipurpose solution daily. Rinse and rub contact lenses to remove proteins daily for at least 20 seconds. Use the recommended contact lens solutions from your eye care provider. Switch to water-based cosmetic products. Also be sure to discard the multipurpose solution at the end of the 90-day usability period. It might be helpful to write an ‘Opened on’ or ‘Discard’ date on the bottle as a reminder.”
b. Maximum number of days the therapy should be employed	“Perform appropriate lens care daily. You also should permanently switch to water-based cosmetics.”
c. Product administration procedures	“If your symptoms do not resolve, then return to your contact lens specialist for a refitting appointment and other options.”
d. Expected time	“Symptoms should resolve within the next day.”

Relevant Evaluation Criteria	Scenario/Model Outcome
to onset of relief	
e. Degree of relief that can be reasonably expected	"The fogginess should disappear with proper cleaning."
f. Most common adverse effects	n/a
g. Adverse effects that warrant medical intervention should they occur	"Fogginess that does not go away warrants medical attention."
h. Patient options in the event that condition worsens or persists	"See your eye care provider if the fogginess persists even after proper cleaning of the lenses, or if eye pain develops, because other issues may potentially be causing the problem."
i. Product storage requirements	"Solution should be stored at room temperature in a dry place. The contact lens case should be allowed to air dry while contact lenses are not in it."
j. Specific nondrug measures	n/a
Solicit follow-up questions from the patient or caregiver.	"What if I don't want to have to do this every day?"
Answer the patient's or caregiver's questions.	"You can call your eye care provider and discuss some options. The provider could potentially change your prescription to daily disposable contact lenses."
Monitor: Follow-up and Evaluate	
9. Assess patient	Call Ms. Smith in 2-3 days to assess how everything is going and if the

Relevant Evaluation Criteria	Scenario/Model Outcome
outcome.	suggestions worked for her. Also determine whether she has any questions.

Key: n/a = Not applicable; NKA = no known allergies.

Case 29–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient calls the pharmacy complaining of severe pain, redness, and blurry vision in both eyes after inserting his contact lenses this morning. He thought that the symptoms would dissipate in a few minutes, but they have persisted. Yesterday, he was switched to a peroxide-based disinfection system for his gas-permeable lenses at his yearly eye exam. Patient reports that he uses only a peroxide disinfecting solution and does not rinse lenses before insertion.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Patient reports that symptoms have subsided only slightly since removal of the lenses.
c. Description of the patient's efforts to relieve	The patient has not tried anything to address the situation other than removing the contacts shortly after insertion.

Relevant Evaluation Criteria	Scenario/Model Outcome
the symptoms	
d. Patient's identity	Thomas Chavez
e. Patient's age, gender, height, and weight	22 years, male, 6 ft 1 in., 200 lb
f. Patient's occupation	Web designer
g. Patient's dietary habits	Patient eats a balanced diet.
h. Patient's sleep habits	Mr. Chavez works long hours, getting about 5-6 hours of sleep per night.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	No other conditions or medications
j. Allergies	Penicillin
k. History of other adverse reactions to medications	None
l. Other (describe) -----	Mr. Chavez is a nonsmoker and drinks socially.
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Toxic keratitis, peroxide solution-induced
3. Identify exclusions for self-treatment.	Possible toxic keratitis
	Pain that does not subside with removal of contact lenses
4. Formulate a comprehensive list of	Options include

Relevant Evaluation Criteria	Scenario/Model Outcome
therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	(1) Refer the patient to an eye care provider.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Inform Mr. Chavez that he needs immediate medical care, either from his eye care provider or in a hospital emergency department, to identify the extent of the problem. He should not use self-care treatment at this time.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Your symptoms suggest that you may have injured your eye, so you need to go to either your eye care provider or a hospital emergency department immediately."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"It is likely that your eye came into contact with un-neutralized peroxide solution from rinsing the contacts with peroxide solution or not allowing the contacts to neutralize overnight for at least 6 hours. Because eye contact with peroxide can cause significant damage, you need to go to either your eye care provider or a hospital emergency department immediately, to prevent any permanent damage, such as vision loss."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	Criterion does not apply in this case.
Solicit follow-up questions from the patient or caregiver.	"I have a busy schedule today—do you think rinsing out my eye will be enough to solve the problem?"

Relevant Evaluation Criteria	Scenario/Model Outcome
Answer the patient's or caregiver's questions.	"Although you should rinse your eye with saline or tap water immediately, this will likely not be enough to ensure that no damage is done. Therefore, you need to be seen by your eye care provider or an emergency department physician as soon as possible. You could suffer permanent damage to your eye if it is not treated immediately."
Monitor: Follow-up and Evaluate	
9. Assess patient outcome.	Call Mr. Chavez in 2-3 days to determine whether he sought medical treatment and how the situation resolved. Ask if he has any further questions.

Patient Counseling for Prevention of Contact Lens–Related Disorders

Patient education on lens insertion and removal should always be provided at the time lenses are fitted. Patients also should be instructed on proper care techniques, with a specific recommendation for a lens care system. Often the prescriber's advice to use a particular product is ignored, and patients select products by price alone, especially with the availability of generic solutions. Similarity of product labels and lack of standardized labeling can lead to further confusion. Patients often ask whether it matters which solution they use. The correct answer is that it *does* matter, because incompatible solutions can be the cause of contact lens complications. Lens care products typically are formulated for use with either soft or GP lenses and, with a few exceptions, should not be used interchangeably. The box "Patient Education for Prevention of Contact Lens–Related Disorders" outlines the care regimen for each type of contact lens.

Patient Education for Prevention of Contact

Lens–Related Disorders

The objective of contact lens care is to prevent lens-related problems such as abrasions or infections of the cornea. For most patients, following the prescribed lens care regimen, product instructions, and self-care measures listed here will help ensure trouble-free use of contact lenses.

General Care Instructions for Most Contact Lens Types

- See [Table 29–2](#). Before handling or caring for contact lenses, wash hands with noncosmetic soap and rinse thoroughly; then dry them with a lint-free towel.
- Each time contact lenses are removed, clean, rinse, and disinfect them before wearing them again.
- Gently rub both surfaces of the contact lens, rinse thoroughly, and soak lenses overnight in the recommended solution according to the eye care provider’s instructions.
- For care of your lenses, use only those contact lens products recommended by the prescribing eye care provider.
- Do not change brands or products unless instructed to do so by the eye care provider. (Not all care systems are alike, and some may not be compatible with the contact lenses prescribed.)
- Do not “top off” a storage solution in the case after the solution has been used.
- Replace soaking or disinfecting solutions in the lens case after each use.
- Store contact lenses in fresh disinfecting solution overnight for the minimum soaking time recommended by the manufacturer to provide adequate disinfection.
- If lenses are worn intermittently, check and replace the solution weekly; consider daily disposable lens wear.
- Discard open bottles of solution if not used within the recommended time frame after being opened. Refer to the package labeling for individual products because “use within” time frames range from 1 up to 3 months, depending on the product. Write the date of first use of the solution on the outside of the

bottle.

- Store contact lenses in a proper lens case when not in use. Clean the contact lens case daily by rubbing with a disinfecting solution and allowing the case to air dry.
- Replace the contact lens case every 3 months.
- Saline solution is used only to rinse lenses; saline will not clean or disinfect contact lenses and should not be used as a storage solution.
- Do not use tap water to rinse contact lenses or to clean cases. Never store lenses in tap water.
- Do not place contact lenses in your mouth to clean or lubricate the lens. This practice can result in eye infections.
- To prevent contamination, do not touch dropper tip or the tip of lens care product containers.
- While lenses are in the eye, use only ophthalmic solutions specifically formulated for contact lens use.
- Avoid swimming, showering, bathing in hot tubs, or rafting or other activities in natural bodies of water while wearing contact lenses unless external eye protection, such as watertight goggles, is used.
- Follow prescribed wearing and replacement schedules.
- Avoid exposing contact lenses to extreme temperatures.
- Avoid use of oily cosmetics while wearing lenses. Bath oils or soaps with an oil or a cream base may leave a film on the hands that will be transferred to the lenses. Apply cosmetics *after* inserting contact lenses.
- To avoid mixing up the lenses, always insert or remove the same lens first. Check hard lenses for a dot in the lens periphery that identifies right from left.
- If a lens is not comfortable after insertion or vision is blurred, check to see if it is on the wrong eye or is inside out (inverted).
- To avoid damaging lenses, either apply aerosol cosmetics, hair products, and deodorants well before lens insertion or keep eyes closed until the air is completely clear of spray particles.
- Except for prescription continuous-wear lenses, do not wear lenses while sleeping.
- To avoid excessive dryness of the eyes, do not wear lenses while

- sitting under a hair dryer, overhead fans, or air ducts.
- When lenses are worn outside on windy days, protect the eyes from soot and other particles, which may become trapped under the lens and scratch the cornea, by wearing sunglasses or other protective eyewear.
 - Use eye protection in industry, sports, or any other occupation or hobby (such as cooking, when dangerous splatter may be an issue) that may be associated with the potential for eye damage.
 - Do not insert lenses in red or irritated eyes. If the eyes become irritated while lenses are being worn, remove the lenses until the irritation subsides. If irritation or redness does not subside, consult an eye care provider.
 - If an eye infection is suspected, see an eye care provider immediately.

Care Instructions for Soft Lenses

- See [Tables 29–2](#) and [29–3](#) for guidelines on cleaning and disinfecting soft lenses.
- Handle soft lenses carefully because they are very fragile and can be torn easily.
- Remove soft lenses before instilling any ophthalmic preparation not specifically intended for concurrent use with such lenses. Wait at least 20–30 minutes before reinserting the lenses, unless directed otherwise by an eye care provider.
- Do not wear lenses when a topical ophthalmic ointment is being used.
- Do not wear soft contact lenses in the presence of irritating fumes or chemicals.

Care Instructions for Gas-Permeable Lenses

- See [Tables 29–2](#) and [29–8](#) for guidelines on cleaning gas-permeable lenses.
- Do not use tap water to rinse off cleaner or to rewet lenses. If exposure to tap water occurs, disinfect lenses before inserting them in the eyes.

- See [Table 29–4](#) for guidelines on using disinfecting systems.

Care Instructions for Continuous-Wear Lenses (Gas-Permeable or Soft)

- Remove mascara before sleeping because it can flake off during sleep, with particles becoming trapped underneath the lens.
- If a lens appears to be lost on awakening, check to see whether the lens was displaced within the affected eye. Soft lenses can fold over on themselves and get lodged underneath the top or bottom eyelid.
- Each morning, check eyes carefully for unusual or persistent redness, discharge, or pain. If redness does not abate within 45 minutes, or if discharge or pain is present, remove the lens and call your eye care provider.
- Check vision after inserting lenses. (Some hazy vision is normal on awakening because of the corneal hypoxia that develops overnight.) Apply a few drops of rewetting solution to improve hydration of the lens and help correct the hypoxia. If the problem is not resolved, remove lenses, clean them, and reinsert. If vision is not improved within an hour, remove lenses and call your eye care prescriber.

Key Points for Prevention of Contact Lens–Related Disorders

- Following the prescribed lens care program is the best strategy for avoiding lens wear–related problems.
- The health care provider should explain the care regimen for the patient’s particular lens type and emphasize the importance of using only the products recommended for the prescribed lenses.
- Instructions on avoiding practices or situations that can cause eye irritation or lens damage also are important in educating the patient about successful wearing of contact lenses:

- Used contact lens solutions should not be “topped off” or reused.
- Even when using no-rub solutions, patients should be counseled to rub and rinse contact lenses to fully remove protein deposits.

- Patient counseling should identify signs and symptoms that indicate the need for medical care. Patients should be informed that if eye redness or pain or blurry vision occurs during wear of any form of contact lens, they should immediately remove the lens and see an eye care provider for evaluation before reinserting the lens.
- Patients should be reminded to have an annual check-up/evaluation by an eye care specialist.

Chapter 30: Otic Disorders

Authors: Deborah Zeitlin

Editor's Note: This chapter is based on the 19th edition chapter of the same title, written by Veronica T. Bandy.

Ear disorders are well-documented reasons for seeking health care in persons of all ages, with greater frequency noted in the pediatric and geriatric age groups than in adults.¹ Otic disorders are responsible for approximately 1.9% of yearly ambulatory care visits.² Specifically, cerumen impaction is one of the top three diagnoses managed by otolaryngologists.¹ Excessive or impacted cerumen is common, and incidence rates are reported as 10% in children, 5% in adults, and greater than 30% in the developmentally challenged and geriatric populations, especially nursing home residents.^{3,4} Approximately 12 million patients visit a primary care provider yearly for cerumen impaction, with more than 8 million requiring removal procedures.^{4,5} This common outpatient procedure cost over \$46 million in 2012 within the Medicare population alone.^{4,5} The primary impact of excessive cerumen is transient hearing loss, which affects patients of all ages.³⁻⁶

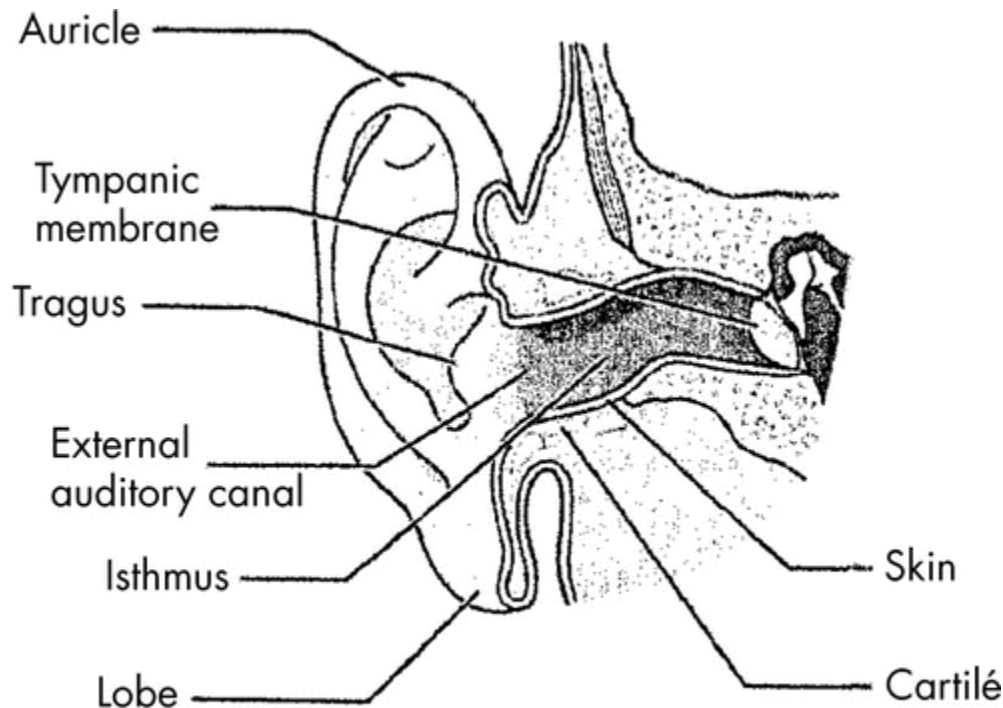
Self-treatment with nonprescription medications and complementary therapies should be restricted to minor external ear disorders, which include disorders of the auricle and the external auditory canal (EAC). Excessive cerumen and water-clogged ears are self-treatable EAC disorders for which the U.S. Food and Drug Administration (FDA) has approved nonprescription otic medications. Other self-treatable disorders of the auricle include atopic dermatitis, seborrhea and psoriasis, and allergic and contact dermatitis. [Chapters 33](#), [34](#), and [35](#), respectively, provide detailed discussions of the etiology and treatment for these disorders.

Head and neck diseases can cause referred pain, which patients often perceive as originating from the ear. The health care provider must attempt to determine the cause of pain before recommending self-treatment or medical referral. This chapter first briefly examines the anatomy of the ear and pathophysiology of ear disorders and then reviews associated nonprescription therapies for excessive or impacted cerumen and water-clogged ears. Next, an approach to the assessment of self-treatable otic disorders is described, with relevant case studies, followed by sections on patient counseling and

evaluation of patient outcomes.

Pathophysiology of Otic Disorders

The anatomy of the ear is conducive to certain types of otic disorders, especially in children; therefore, an overview of the anatomic features is included. The external ear consists of the auricle (pinna), the EAC ([Figure 30–1](#)), and the tympanic membrane (eardrum), which separates the external ear from the middle ear.⁶ The auricle is composed of cartilage with a closely apposed thin layer of highly vascular skin.^{7,8} The lobe has fewer blood vessels and is composed primarily of fatty tissue. The triangular piece of cartilage in front of the ear canal adjacent to the cheek is the tragus.



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FIGURE 30–1 Anatomy of the auricle and external ear.

The EAC consists of an outer cartilaginous portion, which makes up one third to one half of its length, plus an inner body, or osseous portion.^{7,8} At the end of the canal is the tympanic membrane.⁹ The EAC in children is shorter, straighter, and flatter than that in adults, in whom the canal tends to lengthen

and form an S shape. The eustachian tube (within the inner ear) in a child also is shorter and flatter than that in an adult. By adulthood, the eustachian tube lengthens downward from the middle ear to the nasopharynx. This conformation helps promote drainage and inhibits aspiration of pharyngeal and nasal contents into the middle ear, which may help explain why children have more frequent middle ear infections than adults.¹⁰

The skin that covers the auricle is susceptible to bleeding when scratched, because of the lack of flexibility usually afforded by a subcutaneous layer of fat, not present in this location, and the generous blood supply to the area.^{7,8} The skin is highly innervated, resulting in a disproportionate degree of otalgia (ear pain) relative to any inflammation present. Skin farther along the course of the EAC is thicker and contains apocrine and exocrine glands as well as hair follicles. The skin in the canal is continuous with the outer layer of the tympanic membrane.

Cerumen, or earwax, present in the EAC consists of a mixture of sebum, an oily secretion from the exocrine glands, and a milky, fatty fluid from the apocrine glands. It lines the skin surface in the outer half of the EAC and may mix with desquamated cells.⁴ Cerumen lubricates the canal, traps dust and foreign materials, and provides a waxy, waterproof barrier to the entry of pathogens.⁷ Within the cerumen are various antimicrobial substances (lysozymes), and it has an acidic pH, which helps inhibit bacterial and fungal growth.¹¹

The canal skin sheds continuously and mixes with cerumen. The debris-laden cerumen slowly migrates outward with jaw movements (in chewing and talking). This migration serves as a process of self-cleaning.⁴ Cerumen may appear dry and flaky (gray color) or have an oily or paste-like consistency (honey color).¹²

Because the EAC forms a blind cul-de-sac, it is prone to collecting moisture. Its dark, warm, moist environment is ideal for fungal and bacterial growth. In the pre-inflammatory stage, moisture, local trauma, or both can remove the lipid layer covering the skin. Local trauma from fingernails, cotton-tipped swabs, or other items inserted into the canal can abrade the skin, allowing pathogens to enter. Because a normal, healthy ear canal is impervious to potentially pathogenic organisms, skin integrity generally must be interrupted before such microorganisms can produce an infection. Ear trauma from thermal injuries, sports injuries, ear piercing, and poorly fitting or improperly cleaned ear devices or hearing aids all can contribute to the breakdown of the EAC's

natural defenses.⁷ When involving the ear, dermatologic skin disorders, such as contact dermatitis, seborrhea, psoriasis, and malignancies, may also compromise these defenses.¹³

Patients engaging in self-care should be educated on the natural defenses of the ear canal. Considerations include the protective role of cerumen, the importance of maintaining the normal pH (<6.5) of the EAC, and the purpose of the hairs that line the outer half of the canal. The hairs within the ear canal prevent debris from reaching the ear drum, assist with hearing, and maintain a person's balance.

Viral or bacterial ear infections usually manifest as a sore throat, symptoms of the common cold, or an upper respiratory infection and arise in the middle ear behind the tympanic membrane. This presentation is due to the breakdown of natural defenses in the middle and inner ear, especially in younger children, whose immune system is not able to fight off infections as well as adults. These nasopharyngeal secretions can be aspirated and accumulate in the middle ear, leading to bacterial proliferation and an increased risk of infections.¹⁰ Holding back or stifling a sneeze can force secretions into the middle ear and therefore should be strongly discouraged, even in adults.

Excessive or Impacted Cerumen

Cerumen is a naturally occurring substance that assists in the defense of the external ear canal; it is recognized to clean, protect, and lubricate the EAC.⁴ A common myth that all earwax should be removed by cleaning may lead to excessive attempts at clearing the ear canal, with consequent damage to the EAC if done improperly.

Pathophysiology of Excessive or Impacted Cerumen

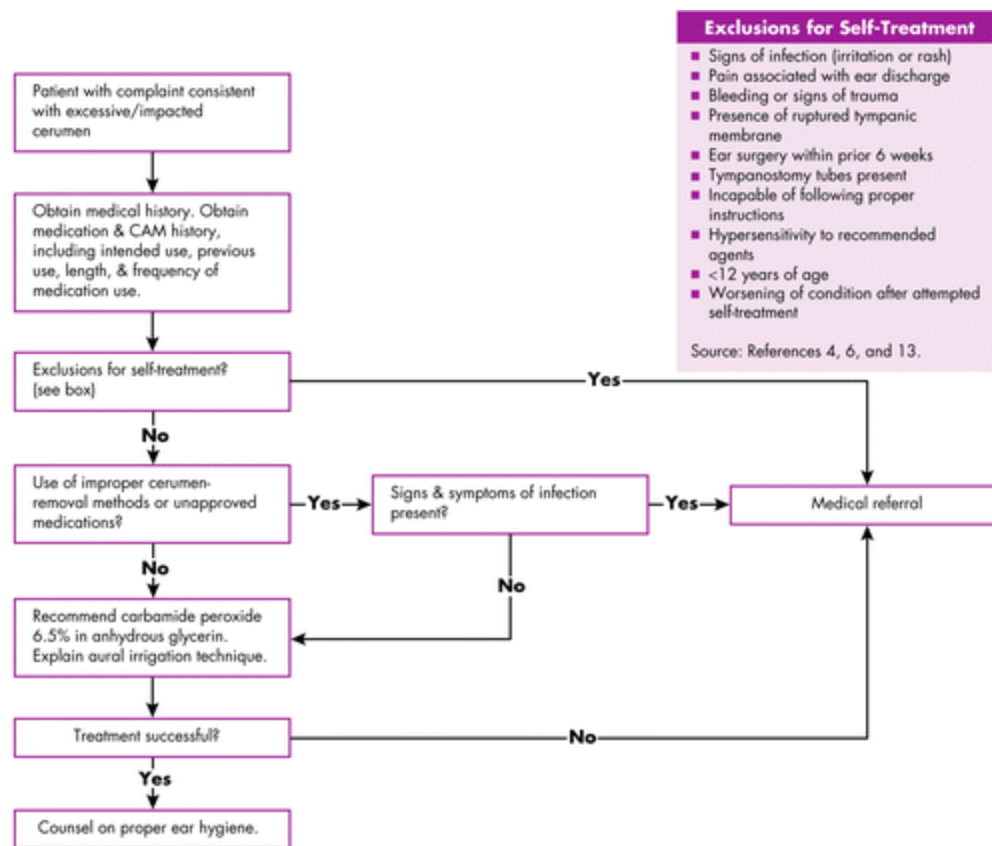
Impacted cerumen is defined as “lodged, wedged, or firmly packed” cerumen in the EAC.⁴ Various factors can disrupt the normal flow of cerumen toward the outer EAC. These causes include anatomic variability resulting in a narrow or irregularly shaped EAC, presence of excessive hair, irritation from foreign

objects used to assist in amplification or blocking of sound (hearing aids or ear plugs), use of cotton-tipped swabs, atrophy of the ceruminous glands with aging, or a genetic tendency.¹⁴⁻¹⁶ Recent research suggests that hearing aid use does not increase the likelihood of cerumen impaction, but more studies need to be performed.¹⁶ Inappropriate methods of removal of excessive or impacted cerumen including use of cotton swabs can push wax deeper into the ear or damage the EAC or tympanic membrane, potentially resulting in otitis media.¹⁵

Clinical Presentation of Excessive or Impacted Cerumen

The sensations of ear fullness, dull pain, or itching may be associated with excessive or impacted cerumen.^{3,4,6,15} Other common symptoms may include discomfort, tinnitus, dizziness, vertigo, cough, hearing loss, and hearing aid malfunction or feedback. Sometimes ear discharge and an odor may be present. Another potential negative effect is impaired cognition, especially in the elderly.

Algorithm: Excessive/Impacted Cerumen



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FIGURE 30–2 Self-care for excessive/impacted cerumen. Key: CAM = Complementary and alternative medicine.

Treatment for Excessive or Impacted Cerumen

Treatment Goals

The goals of treating excessive or impacted cerumen are to remove the cerumen using safe and effective products while preventing potential adverse events. Appropriate use of cerumen removal treatments can be expected to eliminate signs and symptoms specific to the condition and other associated symptoms. The health care provider should assist the patient to choose a product that is cost-effective and readily administered at home.

General Treatment Approach

Therapeutic interventions include the use of cerumen-softening agents with or without irrigation.^{3,4,6} Manual removal of cerumen is an option for primary care providers with the proper skills and instrumentation, but caution is warranted with patient attempts, which are associated with greater risk of EAC damage (bleeding, pain, or perforation).¹¹ The updated clinical practice guidelines state that if the presence of excessive cerumen is asymptomatic, active management is not required.⁴ Manual removal of cerumen is stated as optional rather than recommended treatment.

The earwax-softening agent should be instilled into the ear for the appropriate amount of time, followed by rinsing with warm water, often done using a bulb syringe.¹⁷ Drying of the ear canal can be hastened by gently toweling off the outer ear structures or with use of a handheld blow dryer.¹⁸ Figure 30–2 includes a list of exclusions for self-treatment and presents an algorithm outlining the appropriate self-treatment approach for excessive or impacted cerumen.

Nonpharmacologic Therapy

Earwax should only be removed when it has migrated to the outermost portion of the EAC. The nonpharmacologic method to eliminate cerumen is with an ear-cleaning tool, or curette, for manual earwax removal. The curette can be reused and is only for adult use (e.g., Clinere Ear Cleaners, Ototek Loop Ear Wax Removal Tool). The Clinere Ear Cleaners are marketed only to clean the entrance area of the EAC.^{19,20} Even though the ear cleaners can be inserted into the EAC, caution is indicated because of the associated risk of trauma to the canal skin or tympanic membrane. Warm water irrigation with a bulb syringe is also an option, using sterile water; however, it has not been well studied.⁴ Use of a home oral jet irrigator in the ears is not recommended.⁴ The high-pressure water jet from the irrigator, as well as introduction of copious moisture into the EAC, may potentially cause otitis externa, a perforated tympanic membrane, localized painful injury, vertigo, otitis media, or tinnitus. With attempts to remove cerumen from the EAC, if patients experience pain or bleeding after repeated tries or if symptoms persist, an immediate medical referral is necessary. Medical referral also is warranted and nonprescription treatment is contraindicated in patients with previous ear surgery or a suspected tympanic membrane rupture.^{4,6} The use of cotton-tipped swabs for

ear cleaning or any other product intended for insertion into the EAC may cause increased cerumen impaction with occlusion of the canal and is not recommended in the practice guidelines.⁴ Accordingly, impacted cerumen should be removed only by a properly trained primary care provider.^{4,14}

Pharmacologic Therapy

Currently the only FDA-approved nonprescription earwax-softening agent is carbamide peroxide 6.5% in anhydrous glycerin.²¹ Other cerumen removal products studied include water-based agents that improve water miscibility (choline salicylate, docusate sodium, phenazone, potassium carbonate, urea peroxide, saline, distilled water) or oil-based agents that soften by dissolution (almond oil, benzocaine, chlorbutanol, or triethanolamine polypeptide). Results show that these agents are no more effective than carbamide peroxide and not recommended for use at this time.^{4,22,23}

Carbamide Peroxide

Carbamide peroxide 6.5% in anhydrous glycerin is FDA approved for use in the removal of hardened or impacted cerumen within the EAC. It is neither oil nor water based. It can be used alone or in conjunction with warm water irrigation to remove the loosened cerumen. This product can be used in children 12 years of age and older and adults. Use in patients younger than 12 years should be directed by the advice of a primary care provider.

For correct administration, 5 to 10 drops of the solution are instilled into the affected ear(s), with care to prevent the applicator tip from entering the EAC. Care also is warranted to prevent contact of the solution with the eyes during administration. The solution should remain in the EAC for several minutes for effective softening of excessive earwax. As carbamide peroxide is exposed to moisture, hydrogen peroxide and oxygen release slowly, resulting in a weak antibacterial effect and mechanical loosening of cerumen.

Anhydrous glycerin acts to soften and penetrate cerumen to help loosen excessive earwax. Anhydrous glycerin is widely used as a solvent and vehicle that has both emollient and humectant properties.²⁴ Any cerumen remaining after treatment may be removed with gentle, warm-water irrigation administered with a rubber otic bulb syringe.^{4,25} Earwax removal syringes are now widely marketed, with claims of increased safety and effectiveness

compared with bulb ear syringes. Caution is essential to ensure that the syringe tip is correctly placed and not over-inserted into the EAC.

Carbamide peroxide may be administered twice daily for up to 4 days. Patients should contact a primary care provider if symptoms persist after 4 days of use, if adverse effects develop, or if the presence of infection is suspected. Reported adverse effects include pain, rash, irritation, tenderness, redness, discharge, and dizziness.²⁶

Other Cerumenolytics

Other options to reduce the buildup of cerumen in the EAC include hydrogen peroxide and docusate.⁴ Hydrogen peroxide can be a source of nascent oxygen when exposed to moisture and function as a weak antibacterial agent.²⁷ Hydrogen peroxide 3% has been used to flush the ear canal during procedures for softening or removing earwax.³ Because hydrogen peroxide solutions contain water, overuse may predispose the ear to infection from tissue maceration caused by excessive water left in the EAC. This product is not FDA approved to treat excessive/impacted cerumen. Docusate is also a water-based cerumenolytic and used off-label.³ In comparison of docusate with other such products, no difference was found in rate of adverse effects (discomfort, irritation, pain) or clearance of ear wax.^{4,22} It may improve cerumen clearance relative to no treatment.⁶ Olive oil (sweet oil) drops or sprays are not recommended and are not FDA approved to treat excessive or impacted cerumen.⁴

Product Selection Guidelines

Table 30–1 lists examples of cerumen-softening and other otic products. No nonprescription cerumen-softening agents are approved for patients younger than 12 years. No special consideration for use is necessary in pregnant or lactating women or in older adults.

TABLE 30–1 Selected Nonprescription Products for Otic Disorders	
Trade Name	Primary Ingredient(s)
Cerumen-Softening Products	
Debrox Otic Drops	Carbamide peroxide 6.5%; glycerin; packaged with or without syringe

Trade Name	Primary Ingredient(s)
Earwax Removal	
Murine Ear Wax Removal	Carbamide peroxide 6.5%; glycerin; packaged with or without syringe
Ear-Drying Products	
Auro-Dri Drops	Isopropyl alcohol 95%; anhydrous glycerin 5%
Swim-Ear Drops	Isopropyl alcohol 95%; anhydrous glycerin 5%
Botanical & Homeopathic Products	
Similasan Ear Wax Relief	Causticum 12X; Graphites 15X; Lachesis 12X; Lycopodium 12X
Similasan Earache Relief	Chamomilla 10X; Mercurius solubilis 15X; Sulphur 12X
Hyland's Earache Drops	Belladonna 30C HPUS; Calcarea Carbonica 30C HPUS; Chamomilla 30C HPUS; Lycopodium 30C HPUS; Pulsatilla 30C HPUS; Sulphur 30C HPUS

Key: HPUS = *Homeopathic Pharmacopeia of the United States* (source for ingredients).

Complementary Therapies

An available homeopathic remedy to remove excessive cerumen is the use of ear candles. In accordance with the instructions for such products, a hollow ear candle is inserted into the EAC, and the candle's external protrusion is then lit on fire. It is hypothesized that the flame of the burning candle creates a negative pressure sufficient to draw cerumen from the EAC and into the hollow area of the candle. Currently, clinical practice guidelines advise against this treatment because of potential dangers and injuries associated with this practice. These risks include ear canal obstruction, hearing loss, tympanic membrane perforation, otitis externa, and burns to the patient's hair, face, or ear.⁴ FDA posted a consumer alert and video warning advising against the use of such products.²⁸ Also, the Center for Device and Radiological Health issued an alert notifying that the product labeling is "false and misleading," with no scientific evidence to support the practice.²⁹ For patients who inquire about ear candles, it is important to emphasize the associated risks, because these

candles may be available in pharmacies or on the Internet. (See [Chapters 51](#) and [52](#) for more information on natural products and complementary and alternative therapies.)

Water-Clogged Ears

Water-clogged ears constitutes a disorder defined as the retention of water within the EAC. The prevalence is unknown. This water retention can lead to hearing impairment, localized discomfort, or a sensation of fullness in the ear canal.²¹ Water-clogged ears should not be confused with otitis externa or swimmer's ear. Only isopropyl alcohol 95% in anhydrous glycerin 5% base as the active ingredient is recognized by FDA to be safe and effective when used as an ear-drying agent.²¹ Approved labeling for ear-drying products is limited to statements that may include "dries water in the ears and relieves water-clogged ears after swimming, showering, bathing, washing the hair." Any misleading statements would be considered misbranding.²¹ Of note, these products are approved only to aid in ear drying after such activities and not for prevention of moisture accumulation or treatment of an inflammatory process.

Pathophysiology of Water-Clogged Ears

A few specific host and environmental factors are recognized to contribute to the presence of excessive moisture within the EAC. Physical or anatomic changes within the EAC, such as excessive hair growth and canal narrowing, may lead to wax or debris buildup, which can lead to moisture retention. Excessive moisture may become trapped within the ear from sweating, high humidity, or swimming.¹⁸

Clinical Presentation of Water-Clogged Ears

The presence of water in the ear can cause transient hearing impairment or a sensation of localized discomfort or fullness. Heat and humidity can lead to swelling within the EAC, skin maceration, itching, and possible infection.³⁰ Patients with a history of ear surgery or those experiencing pain, dizziness, or ear drainage, or who display symptoms suggestive of otitis externa, infection,

or inflammation within the EAC, should receive a medical referral.³¹

Algorithm: Water-Clogged Ears

FIGURE 30–3 Self-care for water-clogged ears. Key: CAM = Complementary and alternative medicine.

Treatment of Water-Clogged Ears

Treatment Goals

The goals of treating a water-clogged ear are to dry the EAC using a safe and effective agent and prevent recurrences in persons who are prone to retaining moisture in the ears.

General Treatment Approach

Before recommending an agent to treat water-clogged ears, the health care provider should determine whether the patient has a ruptured tympanic membrane or a tympanostomy tube in place. Ear-drying agents are very painful if instilled in either of these situations. [Figure 30–3](#) includes a list of additional exclusions for self-treatment and presents an algorithm outlining the appropriate self-treatment approach for water-clogged ears.

Nonpharmacologic Therapy

Nonpharmacologic measures include tactics to prevent exposure and accumulation of moisture within the EAC. Earplugs or a bathing cap can be recommended when swimming.^{31–33} A variety of products, intended to protect the ears from exposure to water or absorb water when present, are available including AquaEars, BioEars, and ClearEars. The ClearEars water-absorbing earplugs are inserted into the ear canal to absorb trapped water; adult supervision is required for use in children younger than 11 years. The earplugs are left within the canal for 5 to 10 minutes to absorb any trapped water and then gently removed and discarded.³⁴ One maneuver to dispel excessive

moisture from the ear canal is to pull the ear lobe gently while tilting the head downward; this action straightens the EAC, which promotes gravity drainage.^{29,32,33} Another method is using a blow dryer on the lowest heat setting to help dry the EAC.³² For “waterproofing” the ears, the efficacy of earplugs versus cotton balls coated with petroleum jelly has been evaluated in a simulation study. Inserting petroleum jelly–coated cotton balls in the outer ear canal was found to be adequate initially. However, if expected duration of water exposure will be longer than 15 minutes, earplugs are more effective to prevent water from permeating the EAC.³⁵ One comparative study showed that molded earplugs provide better water leakage prevention than other earplugs or cotton balls covered with petroleum jelly.³⁶

Pharmacologic Therapy

Isopropyl alcohol 95% in anhydrous glycerin 5% is considered a safe and effective “ear-drying aid.”²¹ No minimum age is listed on the ear-drying products generally accepted for use when the ears are exposed to moisture. Patients are instructed to instill 4 or 5 drops in the affected ear. The active ingredient contains a warning to keep the product away from fire, because it is flammable. Instillation into the eyes should be avoided. If pain, burning, or irritation occurs with application or if symptoms persist after several days of use, a medical referral is indicated.³⁴ (See [Table 30–1](#) for examples of products containing these agents.)

Isopropyl Alcohol in Anhydrous Glycerin

Alcohol is highly miscible with water and acts as a drying agent. In concentrations greater than 70%, alcohol is also an effective skin disinfectant.³⁵ Glycerin has been used in pharmaceutical preparations for its solvent, emollient, or hygroscopic properties. It is safe but stings when applied to open wounds or abraded skin. Repeated use of alcohol alone can cause overdrying of tissue in the canal. The combination of alcohol and glycerin, however, provides a product that reduces moisture in the ear without overdrying.

Product Selection Guidelines

[Table 30–1](#) lists examples of ear-drying and other otic products. No special consideration is necessary for use of these preparations in pregnant, lactating, or geriatric patients.

Assessment of Otic Disorders: A Case-Based Approach

The most common complaints in ear disorders are otalgia, pruritus (itching), and hearing loss. Evaluating the characteristics of each particular symptom, such as pain and hearing loss, as well as the specific combination of symptoms, is key to assessing otic disorders. Cases 30–1 and 30–2 provide examples of the assessment of two different patients with otic disorders; common otic symptoms and possible causes are highlighted. **Table 30–2** compares the signs and symptoms and other features of common otic disorders.^{3,4,7,21,33,37–40} **Table 30–3** summarizes common causative disorders and appropriate management for primary presenting complaints related to the ear: otalgia, otic pruritus, hearing loss, dizziness, tinnitus, and foreign body.^{3,7,10,13,18,21,41–44} Screening for hearing is typically performed in newborns or children and adults who present with potential deficits. Routine screening for hearing loss in older adults is currently not recommended, but the U.S. Preventive Services Task Force is reevaluating this issue.⁴⁵ If hearing loss is a concern, it is recommended that the patient seek medical referral.

TABLE 30–2 Differentiation of Common Otic Disorders						
TABLE 30–2 Differentiation of Common Otic Disorders						
Disorder	Etiology	Pain	Itching	Hearing Loss or Hearing	Discharge	Other Features
Ruptured tympanic membrane	Otitis media or trauma to ear such as a sharp blow, diving into water, forceful irrigation of ear	Brief, severe	No	Abrupt	If associated with otitis media	May be associated with otitis media (see that entry)
		Acute				Swollen ear
External otitis (swimmer's ear)	Local trauma to EAC caused by excessive moisture or abrasions; subsequent fungal/bacterial infections	Acute, ranges from mild to severe, with movement of tragus or auricle	Yes	Occasional	Occasionally, clear discharge changing to seropurulent	Swollen ear canal, discharge, swollen lymph nodes, fever, usually occurs in summer or in warm, humid

Disorder	Etiology	Pain	Itching	Loss of Hearing	Discharge	Other Features
		of tragus				stimates or in
		of auricle Sharp,				warm, humid climates Perforated or
Otitis media Otitis media	Bacterial infection of middle ear, infection of both ears can usually help in early infection respiratory tract infection	steady, frequently steady; frequently unilateral; does not increase withagus or auricle	No No	Is sometimes decreased sometimes decreased	Possible exudate through perforated eardrum	bulging Perforated or bulging nodes sometimes lymphadenofever, skin rashes usually no fever, dizziness; usually occurs
	Insects,	of tragus Dull auricle				in winter If obstruction
Foreign object in ear Foreign object in ear	insertion of objects, by insertion of objects by children, attempting to, sound	severe, with sense of fullness with sense of pressure during chewing	Yes Yes	Yes Yes	Possible exudate Possible secondary bacterial infection	not removed from ear acute otitis media and tinnitus may develop.
	attenuators Burns from curling iron,					
Trauma to ear Trauma to ear	Blow to the ear from blunt objects/ injury to the ear from blunt objects, sports injuries, piercing, improper techniques, abrasions of EAC, rashes, abrasions of EAC, rapid changes in air pressure	Ranges from sharp Steady sharp brief and severe to brief and severe	Rare Rare	Varies, can be abrupt Varies, can be abrupt to seldom	Seldom Seldom	Untreated hematomas may cause swelling, may cause tearing, may cause pain, may cause bleeding, may cause infection, may cause metal poisoning, may cause shock syndrome, hepatitis B.
	changes in air pressure disorders,					Continuous or intermittent
Tinnitus Tinnitus	blockage of EAC, exposure to loud noise levels, acoustic	Possible Possible	No No	Sometimes Sometimes	None None	continuous or intermittent ringing, roaring, or

Disorder	Etiology	Pain	Itching	Loss of Hearing	Discharge	Other Features
	EAC exposure to high noise levels, acoustic trauma, (from sulfate, disease, drug toxicity, foci, otitis media, aminoglycosides, and other antibiotics)					hearing as ringing, roaring, or humming
Excessive/impacted cerumen	Overactive sebaceous glands, obstructed migration of cerumen	Rare, dull pain if present	No	Often	None	Sense of fullness or pressure in ears
Excessive/impacted cerumen	Obstructed glands	Rare, dull pain if present	No	Often	None	Sense of fullness or pressure in ears
Water-clogged ears	migration of excessive cerumen moisture in EAC	None	No	Often	None	Sense of fullness or wetness
Water-clogged ears	Excessive moisture in EAC	None	No	Often	None	Sense of fullness or wetness

Key: EAC = External auditory canal.

TABLE 30–3 Etiology and Treatment of Common Otic Complaints

Complaint	Etiology	Treatment
Otalgia	<i>Intrinsic:</i> infection, trauma, foreign objects, perichondritis <i>Extrinsic:</i> dental or jaw problems, nasopharyngeal infections, tumors, cysts, migraine headaches, neuralgias, cervical arthritis	Medical referral unless cause is clearly obvious, self-limiting, and self-treatable; always refer patients with suspected infection; self-care may delay seeking proper treatment.
Otic pruritus	Seborrhea, psoriasis, contact dermatitis; infection (external otitis); excessive dryness related to decreased sebum production	See Chapters 34 and 35 ; medical referral is indicated for suspected infection; excessive dryness: administer 1–2 drops of mineral oil.

Complaint	Etiology	Treatment
Hearing loss	Foreign objects or water trapped in EAC; infection, congestion, neoplasms, tympanic membrane perforation, medication effects; excessive pressure or cerumen in EAC, or exposure to high noise levels	Medical referral is indicated unless hearing loss is related to excessive water or impacted cerumen in EAC.
Dizziness	Inner ear lesions, otitis media, rapid change in pressure on the tympanic membrane, migraine headache, ototoxic drugs, postural hypotension, cardiac disease, neoplasms, irrigation of ear canal with very hot or cold water, motion sickness	Medical referral is indicated unless complaint is related to motion sickness.
Tinnitus	See Table 30-2	Check for impacted cerumen; otherwise, medical referral is indicated.
Foreign body	Insects, beads, seeds, small batteries, or other objects in ear canal	Medical referral; mineral oil can be used to quickly suffocate an insect, with relief of distressing symptoms, until it can be removed by a PCP; moisture causes seeds to swell, making removal more difficult.

Key: EAC = External auditory canal; PCP = primary care provider.

Case 30-1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s)	For the last 2 days, the patient has noticed ear itching and

Relevant Evaluation Criteria	Scenario/Model Outcome
(i.e., nature, onset, duration, severity, associated symptoms)	hearing changes in that sounds are muffled.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	He started a new workout routine and has been wearing ear buds longer than normal during his workouts. He denies any pain, dizziness, or tinnitus.
c. Description of the patient's efforts to relieve the symptoms	He wipes his ears with a dry towel after showering.
d. Patient's identity	Patrick Walker
e. Patient's age, gender, height, and weight	32 years, male, 5 ft 10 in., 180 lb (82 kg)
f. Patient's occupation	Mr. Walker is a financial advisor.
g. Patient's dietary habits	He eats out most meals, primarily fast food. He wants to start making healthier choices.
h. Patient's sleep habits	He averages 6 hours at night owing to his busy work schedule.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Loratidine 10-mg tablet, oral, daily Multivitamin 1 tablet, oral, daily Acetaminophen 1 or 2 500-mg tablets, oral, as needed for pain
j. Allergies	Seasonal allergies in the spring
k. History of other adverse reactions to medications	Amoxicillin and peanuts
l. Other (describe) _____	Mr. Walker currently wants to work out more and lose weight. He started a routine 5 days ago with a plan to run 4 days a week and do strength training twice per week. He wears ear buds when he works out.
Assess	

Relevant Evaluation Criteria	Scenario/Model Outcome
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s) (Table 30-2).	Mr. Walker is experiencing cerumen impaction, likely the result of wearing ear buds more frequently when working out.
3. Identify exclusions for self-treatment (Figure 30-2).	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer the patient to an appropriate PCP. (2) Recommend a nonprescription cerumen-softening agent with proper ear hygiene (Table 30-1). (3) Recommend use of a nonprescription ear-drying agent (Table 30-1). (4) Recommend self-care until the patient can see an appropriate PCP. (5) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Mr. Walker can use a nonprescription cerumen-softening agent with proper ear hygiene and nonpharmacologic therapy.
6. Describe the recommended therapeutic approach to the patient or caregiver.	The patient can use carbamide peroxide 6.5% in anhydrous glycerin 5 to 10 drops up to twice daily as needed for a maximum of 4 days. He also can use a curette as needed to help remove cerumen that is located in the outer part of the ear canal.
7. Explain to the patient or caregiver the rationale for selecting the recommended	"The carbamide peroxide will help loosen the excess cerumen in the outer part of the ear canal and help the cerumen move down the ear canal on its own. A curette can help remove the

Relevant Evaluation Criteria	Scenario/Model Outcome
therapeutic approach from the considered therapeutic alternatives.	excess cerumen once it leaves the ear canal to prevent cerumen impaction.”
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	“You can use a wet washcloth on the outside of the ear canal to help remove excessive earwax or use a curette as needed.” See the box “Patient Education for Self-Treatable Otic Disorders.”
a. Appropriate dose and frequency of administration	“Administer 5 to 10 drops of the carbamide peroxide in anhydrous glycerin into both ears, up to twice daily.”
b. Maximum number of days the therapy should be employed	“It can be used for up to 4 days as needed.”
c. Product administration procedures	“Tilt your head sideways. Instill ear drops using the applicator tips. Make sure that the applicator tip does not enter the ear canal. Keep drops in the ear for several minutes (up to 5 minutes) by keeping your head tilted or placing a piece of cotton at the end of the outer ear canal. After instillation of carbamide peroxide drops, the outer part of the ear canal can be gently flushed with warm water using a soft rubber bulb syringe.”
d. Expected time to onset of relief	“Relief may occur shortly after the first administration; however, this depends on the amount of earwax that is located in the ear canal and the dryness of the earwax.”
e. Degree of relief that can be reasonably expected	“Complete relief can be expected in a few days.”
f. Most common adverse effects	“Side effects usually do not occur with use of this product. Instilling the drops into the ears may cause local irritation.”
g. Adverse effects that warrant medical intervention should they occur	“If you experience pain, rash, irritation, tenderness, redness, discharge, or dizziness when using this product, it is recommended that you contact your PCP.”

Relevant Evaluation Criteria	Scenario/Model Outcome
h. Patient options in the event that condition worsens or persists	"Stop using the product immediately and see your PCP."
i. Product storage requirements	Keep cap on bottle when not using it. Store drops in original carton at room temperature, and do not store above 77°F (25°C).
j. Specific nondrug measures	See the box "Patient Education for Self-Treatable Otic Disorders."
Solicit follow-up questions from the patient or caregiver.	"Should I stop using ear buds?"
Answer the patient's or caregiver's questions.	"You can continue to wear the ear buds, but be aware of the effect of increased earwax. Make sure that you clean off the ear buds after each use and follow the package insert for directions. Always use safe ear hygiene techniques to minimize the risk of earwax impaction."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Mr. Walker in 4 days to evaluate his response to treatment and resolution of symptoms. If he is still complaining of symptoms, he will require a referral to a PCP.

Key: PCP = Primary care provider.

Case 30–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	

Relevant Evaluation Criteria	Scenario/Model Outcome
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient returned from a trip to a beach resort yesterday. Symptoms started on the flight home and include ear discomfort, a sense of fullness, and impaired hearing. Patient also describes a "water-logged" feeling of excess moisture in both ears and reports intermittent ear pain with discharge.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Patient spent a lot of time swimming at the beach and being outside in hot and humid weather.
c. Description of the patient's efforts to relieve the symptoms	Patient has used cotton-tipped swabs in the ear canal to dry them, but this has been unsuccessful at relieving the "water-logged" feeling.
d. Patient's identity	Angela Baker
e. Patient's age, gender, height, and weight	46 years, female, 5 ft 6 in., 145 lb (66 kg)
f. Patient's occupation	Office manager
g. Patient's dietary habits	Ms. Baker brings her lunch from home daily and prepares most of her meals at home. She states she tries to make healthy food choices. She eats out with friends on the weekends for dinner, usually on Friday and Saturday nights. She drinks 1 cup of coffee daily.
h. Patient's sleep habits	She sleeps 7 hours a night on weekdays but is able to sleep 8 hours a night on the weekends.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Omeprazole 20-mg capsule orally daily as needed. Melatonin 1-mg tablet orally at night for sleep. Occasional heartburn and insomnia.
j. Allergies	None
k. History of other adverse	Codeine

Relevant Evaluation Criteria	Scenario/Model Outcome
reactions to medications	
I. Other (describe) _____	Patient currently wants to be able to hear better and eliminate the moist feeling from her ears. It has made it very hard to hear at work and to speak on the phone.
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s) (Table 30-2).	Ms. Baker is experiencing a sensation of water-clogged ears with pain and discharge from both ears.
3. Identify exclusions for self-treatment (Figure 30-3).	Ear pain and ear discharge from both ears
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer the patient to an appropriate PCP. (2) Recommend a nonprescription cerumen-softening agent with proper ear hygiene (Table 30-1). (3) Recommend use of a nonprescription ear-drying agent (Table 30-1). (4) Recommend self-care until the patient can see an appropriate PCP. (5) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Ms. Baker should be referred to a PCP because of symptoms of ear pain and ear discharge. It should also be recommended that patient avoid using cotton-tipped swabs in the ears.
6. Describe the recommended therapeutic approach to the patient or caregiver.	Refer Ms. Baker to a PCP for an appointment today.

Relevant Evaluation Criteria	Scenario/Model Outcome
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Your symptoms suggest you have excess moisture in your ears. Of greater concern are your ear pain and ear discharge, which is not normal. It is highly recommended that you be seen by a PCP to make sure your ears are looked at and treated appropriately."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	"You can use earplugs in the future when you swim to prevent water from getting into your ears." See the box "Patient Education for Self-Treatable Otic Disorders."
Solicit follow-up questions from the patient or caregiver.	"What can I do to prevent this from happening in the future?"
Answer the patient's or caregiver's questions.	"When you go on vacation and know that you will be in a hot and humid environment or swimming more than normal, you can wear molded earplugs to prevent water from entering into your ear canal. After you swim, you can tilt your head to the side and help the excess water drip out of your ears. You can also dry your ear canal by using a blow drier on the lowest heat setting."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Ms. Baker in 1 day to confirm she followed up with her PCP and to determine the current status of her symptoms.

Key: PCP = Primary care provider.

Patient Counseling for Otic Disorders

For patients attempting to self-treat otic disorders, it is important to ensure that they know which medication to use and that the product is appropriate for otic administration, as well as how to administer the agent. They also should demonstrate knowledge of appropriate technique for any otic devices (bulb syringe or curette). Patients should also be aware of the associated risk for injury to the EAC. The health care provider should discourage common harmful practices of relieving itching of the ear using cotton swabs, fingernails, or other devices, and provide instruction on the proper methods of removing excessive cerumen and moisture from the ears. Patients who are susceptible to these disorders should be advised to incorporate proper removal methods in their “aural hygiene” regimen. The health care provider should explain possible adverse effects of all recommended medications and when a medical referral is appropriate. The box “Patient Education for Self-Treatable Otic Disorders” lists specific information to provide in patient counseling.

Evaluation of Patient Outcomes for Otic Disorders

The recommended self-treatment measures for impacted or excessive cerumen and water-clogged ears have been proved effective in most uncomplicated cases. If symptoms related to these conditions persist or worsen after 4 days of appropriate self-treatment, the patient should seek medical referral. Another important indication for medical referral to a primary care provider is the development of ear pain or ear discharge or drainage during treatment.

The health care provider can follow up with the patient by telephone in 4 days to determine whether the therapy is successful, or direct the patient to seek further medical evaluation as appropriate.

Patient Education for Self-Treatable Otic Disorders

Excessive or Impacted Cerumen

Cerumen is necessary to lubricate the ear canal, trap dust and foreign materials, and provide a waxy, waterproof barrier to the entry to prevent infections. The objective of self-treatment is to soften and remove any waxy buildup or to prevent the disorder from recurring in susceptible persons. For most patients, carefully following product instructions and self-care measures listed here will help ensure optimal therapeutic outcomes.

Nondrug Measures

- Use a wet washcloth draped over a finger to remove earwax from the outer canal or an approved ear-cleaning tool following the product instructions.
- Do not insert objects including cotton swabs into the ear to remove earwax. This may injure the ear canal or push the wax farther into the canal.
- Never use an ear candle to remove earwax. This practice can cause serious ear injury or burns to other areas of the body.

Nonprescription Medications

- A combination of carbamide peroxide and anhydrous glycerin is recommended to soften and mechanically break down excessive or impacted cerumen.
- Carbamide peroxide is given by instilling 5–10 drops into the ear that has excessive or impacted earwax twice daily. The patient's head should be tilted and drops placed into the ear canal. The patient should remain in position for 5 minutes.
- Do not let the medication come into contact with the eyes.
- Do not use this medication if you have a fever, ear drainage, pain more severe than a dull pain, dizziness, or a ruptured eardrum, or have had ear surgery within the past 6 weeks.
- Do not use this medication to treat inflamed ear tissue, swimmer's ear, or itching of the ear canal.
- Prolonged contact between carbamide peroxide solution and the

skin of the ear canal can cause dermatitis. Discontinue treatment if irritation or a rash appears.

- Store product in a cool, dry area, and check expiration date before using.

When to Seek Medical Attention

- Monitor for changes in your hearing and symptoms of infection such as pain and itching.
- If severe pain occurs or your hearing worsens, see a primary care provider immediately. Severe pain may indicate a ruptured eardrum.
- If you used carbamide peroxide for 4 days and are still experiencing symptoms, see a primary care provider.
- Patients younger than 12 years of age with ear symptoms also should see a primary care provider.

Water-Clogged Ears

Water can become trapped in the ear, causing a sense of fullness or wetness. The goal of self-treatment is to remove excess moisture from the ear canal or to prevent water from remaining in the ear canal in persons who are prone to this condition. For most patients, carefully following product instructions and the self-care measures will help prevent or treat this condition and ensure optimal therapeutic outcomes.

Nondrug Measures

- Tilt the head with the affected ear down, and gently manipulate the outer ear to help drain water from the ear. Gently towel dry the outer ear area.
- Immediately after swimming or bathing, use a blow dryer on low-heat and low-speed settings to help dry the ear canal. Do not blow air directly into the ear.
- Wear earplugs, preferably molded earplugs, or a bathing cap when ears will be exposed to water for an extended period of time for either bathing, showering, or swimming.

Nonprescription Medications

- Use an isopropyl alcohol 95% in anhydrous glycerin 5% product that is an FDA-approved formulation.
- Do not use this medication if you have a ruptured eardrum or a tympanostomy tube in place.
- Instill 4 or 5 drops in each affected ear. Allow the solution to remain for 1–2 minutes.
- Do not let the medication come into contact with the eyes.
- Keep medication away from fire and flames.
- Store product in a cool, dry area, and check expiration date before using.
- This product is safe for use in children.

When to Seek Medical Attention

- See a primary care provider if you develop pain, burning, or irritation of the ear with medication use.
- See a primary care provider if you have ear drainage or discharge, dizziness, or recent ear surgery,

Key Points for Otic Disorders

- Limit self-treatment of otic disorders to relief of minor symptoms such as a sense of fullness, pressure, or wetness in the ears.
- Seek a medical referral for further evaluation in patients younger than 12 years of age with impacted cerumen, as well as those with signs and symptoms of ear infection, bleeding or signs of trauma, tympanostomy tubes, or ruptured tympanic membrane and patients who had ear surgery within the past 6 weeks.
- Instruct patients on how to use specific otic products that are proved safe and effective.
- Advise patients with self-treatable symptoms to contact a primary

care provider if symptoms worsen or no improvement occurs after 4 days.

- Educate patients about proper ear hygiene, along with the role of cerumen in the healthy ear canal, to prevent further problems.

Chapter 31: Prevention of Hygiene-Related Oral Disorders

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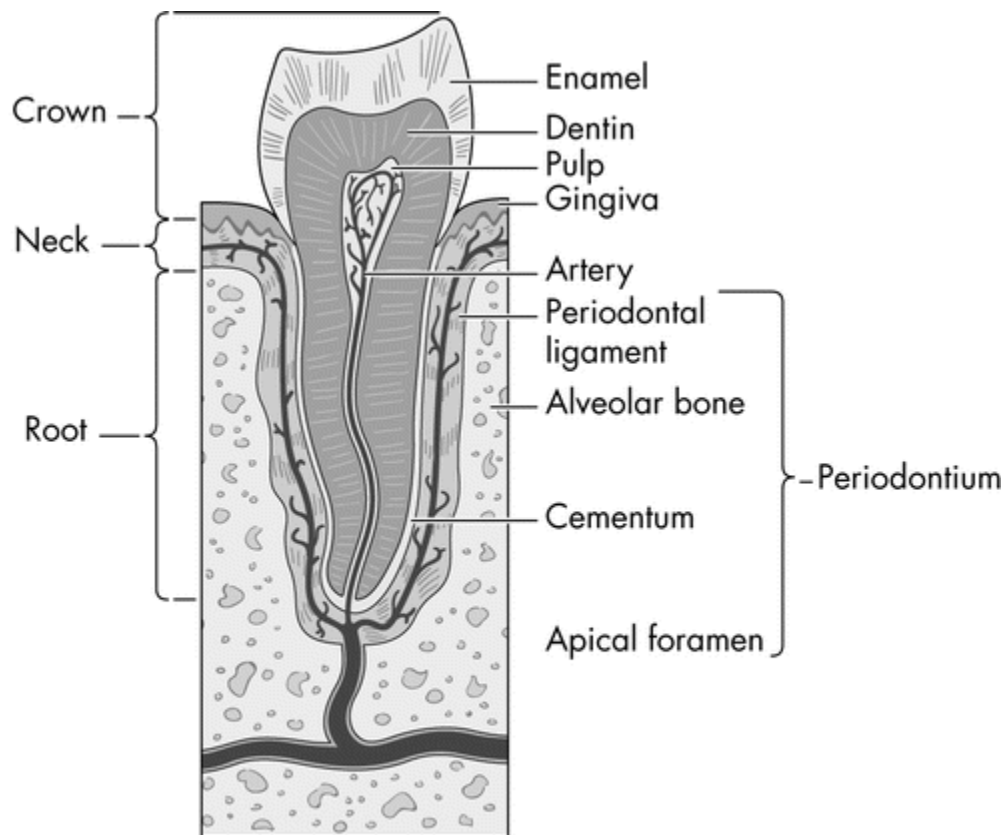
Dental diseases and disorders are recognized to affect the health and well-being of Americans throughout their lifespan. Professional dental care is essential to maintain oral health. The most commonly recommended interval of examination is every 6 months; however, this frequency should be individualized according to historical, clinical, and radiographic findings. Patients at high risk for periodontal disease need more frequent visits, and low-risk patients are recommended to return for follow-up assessments at a minimum of once a year. Children should have their first visit to a dental care provider at the time of the first tooth eruption, at no later than 12 months of age. Despite these recommendations for optimal oral health, more than 30% of adults have not visited a dentist in the past year.¹ By comparison, approximately 85% of children 2–17 years of age have been seen by a dentist within the year.¹ In the United States, 46% of children 2–19 years of age have dental caries, and 13% of these cases go untreated.² The overall frequency of dental caries increases as children get older, from 21% for those 2–5 years of age to greater than 50% for school-age children.² Furthermore, rates of dental caries in Hispanic children and non-Hispanic black children, at 57% and 48%, respectively, are significantly higher than those in non-Hispanic white youth.² Significant disparities in caries frequency also are correlated with socioeconomic status. Poor oral health is particularly detrimental for children in that it affects nutrition, growth, and development.

Improper oral hygiene is a direct cause of dental caries, periodontal disease (gingivitis and periodontitis), halitosis, and some cases of denture-related discomfort. Nonprescription products for prevention of oral disease are widely available in pharmacies, food stores, and other retail venues; educating the public about proper use of these products is key to preventing dental diseases.

The teeth and supporting structures are necessary for effective mastication and articulation, as well as for normal appearance. The primary (deciduous or baby) dentition first appears at the age of approximately 6 months, when the mandibular (lower jaw) central incisors erupt; the process usually is complete with eruption of the upper second molars at approximately 24 months of age.

Each of the upper and lower arches holds 10 deciduous teeth, for a total of 20. Generally, emergence of the permanent dentition (adult teeth) begins when the mandibular first molar erupts behind the deciduous second molar at the age of approximately 6 years, and the process continues in a regular pattern, usually with replacement of deciduous teeth as they are shed. Of the 32 total permanent teeth, 28 usually are present by the age of 14 years; third molars (wisdom teeth) may appear between the ages of 17 and 21 years.

Anatomically, the teeth are viewed grossly as having two parts, the roots and the crown ([Figure 31-1](#)). The roots, which extend below the gingival (gum) line or margin and thus are normally concealed from view, are essential in supporting and attaching the tooth to the surrounding tissues. The crown is the part of the tooth visible above the gingival margin and provides appropriate surfaces for effective mastication. Each tooth has four major structural components: enamel, dentin, pulp, and cementum.



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FIGURE 31-1 Anatomy of the tooth.

Enamel is composed of very hard, crystalline calcium phosphate salts (hydroxyapatite). It is 1.5–2 mm thick at its thickest part and protects the underlying tooth structure. It covers the crown of the tooth, ending around the gum line at the cemento-enamel junction. Enamel's hardness enables the crown to withstand the wear of mastication. *Dentin*, which is softer, lies just beneath the enamel and makes up the largest part of the tooth structure. It contains a network of microscopic tubules that transport nutrients from the dental pulp. Dentin protects the dental pulp from mechanical, thermal, and chemical irritation. The bone-like *cementum* is softer than dentin and covers the root of the tooth, extending apically from the cemento-enamel junction.

The *pulp* occupies the pulp chamber and canal. It is continuous with the tissues surrounding the tooth by an opening at the apex of the root (apical foramen). The pulp consists primarily of vascular and neural tissues. The only nerve endings in the pulp are free nerve endings; therefore, any type of stimulus to the pulp is interpreted as pain.

The *periodontium* comprises the hard and soft tissues that surround the teeth, including the periodontal ligament, the encompassing alveolar bone, and the gingiva. The tooth is suspended hammock-like in bone by the *periodontal ligament*. The cementum's major function is as a surface for attachment of the tooth to the periodontal ligament by periodontal fibers. The periodontal ligament is connective tissue that attaches the tooth to the surrounding alveolar bone and gingival tissue. The periodontal ligament performs supportive, formative, sensory, and nutritive functions. The *alveolar bone* forms the sockets of the teeth. The *gingiva* is the soft tissue surrounding the teeth. Gingiva is categorized as either attached gingiva or unattached gingiva. Attached gingiva normally is pink and stippled (like an orange peel) and is attached to the cementum by periodontal ligament fibers. Unattached gingiva appears light pink or coral in color, is not bound to the underlying tissue of the tooth, and is the first tissue to respond to inflammation.

The major salivary glands—parotid, submandibular, and sublingual—are responsible for secreting *saliva*, an alkaline, slightly viscous, clear secretion that contains enzymes (lysozymes and ptyalin), albumin, epithelial mucin (a mucopolysaccharide), immunoglobulin, leukocytes, and minerals. Normal salivary gland function promotes good oral health in several ways. First, saliva lubricates and facilitates the removal of carbohydrates and microorganisms from the oral cavity. Second, saliva also buffers the decline in pH caused by the

acid formed by carbohydrate fermentation. Third, the mineral components of saliva have a protective role in the demineralization and remineralization of tooth enamel.

Caries

Although the period spanning 2011–2012 through 2015–2016 saw a decrease in dental caries among children in the United States, this improvement was statistically nonsignificant, and caries remains a major public health concern.² Strategies that have been successful in reducing caries include fluoridation of the municipal water supply, topical fluoride treatments, education on proper tooth brushing with a fluoride dentifrice, mouth rinses, daily flossing, a proper diet, and regular dental office visits.⁴

Patients with poor oral hygiene are at greatest risk for developing caries. Other risk factors for the development of caries include presence of orthodontic appliances, xerostomia (dry mouth), use of tobacco products, frequent alcohol use, diabetes, and gum tissue recession that exposes root surfaces. Certain medications may cause xerostomia (see [Chapter 32](#)); this condition also is more likely to develop in patients who have undergone head and neck radiation therapy.

Access to dental care has improved over the last few years, with approximately 77% of the U.S. population covered for such care in 2016, compared with only 55% in 2011.⁵ This increase is likely attributable to the recent expansion of access for adults on Medicaid insurance. Nevertheless, disparities remain, particularly with respect to racial and ethnic minorities and people older than 65 years. In 2015 only about 34% of patients with Medicare insurance had dental benefits, either purchased through individual dental care coverage or available as a supplemental benefit on a Medicare Advantage plan.⁶ For all Americans, access often is limited owing to financial barriers, with prioritization of health crises and basic living needs. Access also may be influenced by government legislation pertaining to health insurance coverage. The Affordable Care Act specified that dental care for children is an Essential Health Benefit; however, purchasing a dental plan was not mandatory under federal law, and ultimately the decision was left up to the family.⁷ The American Health Care Act (AHCA) would allow states to choose which Essential Health Benefits to cover; this coverage would begin in 2020. The impact of the

AHCA, if ultimately passed, on dental care is unknown: Although uninsured rates could potentially increase if Medicaid is converted to a block grant program, the use of health savings accounts to cover dental care may become more widespread.⁸ Delayed access to dental care for children adversely affects not only their oral health but also their general health, well-being, and readiness to start school.

Pathophysiology of Caries

Dental caries is considered an infectious disease that affects the calcified tissues of the teeth. Certain plaque bacteria generate acid from dietary carbohydrates, which demineralizes tooth enamel and dentin, leading to the formation of soft carious lesions (areas of altered calcification or decay evident as pits that, if left untreated, will eventually destroy the tooth). Formation of dental caries requires growth and attachment of cariogenic microorganisms of various species (e.g., *Streptococcus mutans*, *Lactobacillus casei*, *Actinomyces viscosus*) to exposed tooth surfaces. If oral hygiene is neglected, dental plaque (the biofilm containing these organisms) remains on the tooth surfaces and over time attracts more bacteria, thereby promoting decay.

The carious process is characterized by an imbalance between the usual cycle of destruction (demineralization) and repair (remineralization).

Demineralization is caused by organic acids (e.g., lactic and formic acids), which are produced (usually anaerobically) by microbial metabolism of low-molecular-weight carbohydrates (sugars) that readily diffuse into plaque. The resulting reduction in pH on the tooth surface leads to demineralization of dental enamel. Saliva, which is rich in calcium and phosphate ions, is crucial in remineralizing enamel in early changes involved in developing carious lesions. The presence of fluoride ions in the mouth also promotes remineralization and slows demineralization, thereby retarding enamel dissolution.

A carious lesion starts slowly on the enamel surface and initially produces no clinical symptoms. Once demineralization progresses through the enamel to the softer dentin, the destruction proceeds much more rapidly, becoming clinically or radiographically evident as a carious lesion. At this point, the patient can become aware of the lesion either by observing it or by experiencing symptoms of sensitivity to stimuli (e.g., heat, cold, sweet foods) or chewing. If untreated, the carious lesion can progress to involve the dental

pulp (with continuous pain as a common symptom), with eventual necrosis of vital pulp tissue. In addition to pain and difficulty chewing, untreated caries can lead to abscess formation, tooth loss, and serious infections.

Clinical Presentation of Caries

Plaque is commonly recognized as the source of microbes that cause caries and periodontal disease. After meals, food residue may be incorporated into plaque by bacterial degradation. Left undisturbed, plaque thickens, and bacteria proliferate. Plaque growth begins in protected cracks and fissures and along the gingival margin. If not removed within 24 hours, dental plaque (especially in areas opposite the salivary glands) begins to calcify by calcium salt precipitation from the saliva, forming calculus, or tartar. This hardened, adherent deposit is removable only by professional dental cleaning.

Calculus is generally considered to be a substrate on which additional plaque can develop and is not considered the primary causative factor in periodontal disease. However, most periodontists agree that supragingival and subgingival calculus (located above and below the gingival margins, respectively) can promote the progression of periodontal disease by accumulating new bacterial plaque in contact with sensitive tissue sites and by interfering locally with dental self-hygiene efforts to remove plaque.

Prevention of Caries

General Approach

The key to preventing caries is controlling dental plaque. Because a combination of diet high in carbohydrates, oral bacteria, and host resistance is involved in developing caries, prevention should be aimed at modifying these factors. The amount and frequency of refined carbohydrate intake should be reduced; plaque should be regularly removed, usually by mechanical means (e.g., brushing, flossing); and host resistance should be increased through appropriate exposure to fluoride ion.

The declining prevalence of dental caries in permanent teeth among youths,

adolescents, and most adults in the United States may be attributed to a combination of interventions such as increased exposure to fluoride in drinking water, dentifrices, and mouth rinses; changed patterns of diet; and overall improved oral hygiene.

Mechanical removal (brushing with a dentifrice and flossing) and chemical management (e.g., using specific products to prevent plaque accumulation or aid its removal) are two methods used to manage plaque. Plaque on interproximal (between the teeth) surfaces can be removed efficiently only with dental floss and other interdental cleaning aids (e.g., interproximal brush, dental tape, tapered picks).

Nonpharmacologic Therapy

Dietary Measures

Cariogenic foods and beverages, which predispose the tooth enamel to deleterious effects (i.e., erosion), should be avoided in favor of those that are less cariogenic. A food is considered highly cariogenic if it contains more than 15% sugar, clings to the teeth, and tends to remain in the mouth after it is chewed. Conversely, foods are less cariogenic if they have a high water content (e.g., fresh fruit), stimulate the flow of saliva (e.g., carrots, other fibrous foods that require a lot of chewing), or are high in protein (e.g., dairy products). Both the water content of fresh fruit and the resulting flow of saliva tend to wash away the fruit's sugar and neutralize the acid it creates. Milk protein also raises pH and tends to inhibit binding of bacteria. Chewing sugarless gum for 20 minutes after meals can also help reduce tooth decay as an adjunct to brushing and flossing in adults and children older than 5 years of age.⁹ The associated increase in salivary flow helps wash out food debris, and saliva neutralizes acid produced by plaque bacteria.

Plaque Removal Devices

Toothbrushes, dental floss, oral irrigating devices, and specialty aids (e.g., interproximal dental brushes) are the primary devices used in facilitating plaque removal. To ensure the health of teeth and gingival tissues, the American Dental Association (ADA) recommends brushing at least twice daily and flossing at least once daily.

Toothbrushes

The toothbrush is the most universally accepted device available for removing dental plaque and maintaining good oral hygiene. Toothbrushing removes plaque from the lingual (tongue side), buccal (cheek side), and occlusal (biting) surfaces of the teeth. Thoroughness of plaque removal without gingival trauma is more important than the method used. [Table 31-1](#) describes the proper method of brushing teeth.

TABLE 31-1 Guidelines for Brushing Teeth
• Brush teeth after each meal or at least twice a day. • If using toothpaste, apply a small amount of paste to the toothbrush. • Use a gentle scrubbing motion, with the bristle tips held at a 45-degree angle against the gum line so that the tips of the brush do the cleaning. • Do not use excessive force because it may result in bristle damage, cervical abrasion, irritation of delicate gingival tissue, or gingival recession with associated hypersensitivity. • Brush for at least 2 minutes, cleaning all tooth surfaces systematically. • Gently brush the upper surface of the tongue to help remove debris, plaque, and bacteria that can cause oral hygiene problems. • Rinse the mouth, and spit out all of the water (do not swallow).

Manual toothbrushes vary in size, shape, texture, and design, with new product designs proliferating rapidly. These toothbrushes have either nylon or natural bristles that usually are rated as soft, medium, or firm.

Powered toothbrushes, which are widely available on the market, either are battery-operated or have a rechargeable battery system. Battery-operated devices (e.g., Arm & Hammer Spinbrush, quip Electric Toothbrush) use a rotary and/or vibratory motion and are less expensive, but their effectiveness deteriorates over time as the disposable battery loses power. Rechargeable battery toothbrushes may also use a rotary and/or vibrating motion (e.g., Oral B) or ultrasonic vibration (e.g., Sonicare, Oral B) to remove plaque. These powered brushes tend to be more expensive, but they maintain constant effectiveness because of their rechargeability. Powered toothbrushes may be of benefit for certain patients, such as those who are disabled or who have dexterity issues.

Although no definite guideline specifies how often to buy a new toothbrush, ADA recommends that the patient replace the toothbrush every 3–4 months. Two compelling reasons are recognized for replacing toothbrushes frequently: bristle wear and bacterial accumulation. Because different brushing methods cause bristles to wear differently and worn, bent, or matted bristles do not remove plaque effectively, toothbrushes should be replaced at the first sign of bristle wear. Some brands of toothbrushes have color-impregnated bristles that indicate the need for replacement when the color disappears halfway down the bristles.

Product Selection Guidelines. Health care providers should recommend toothbrushes that are ADA approved, as described in the box “American Dental Association (ADA) Seal of Acceptance.”¹⁰ ADA criteria for acceptance are based on safety and efficacy concerns. Available evidence indicates that powered toothbrushes can provide a statistically significant reduction in the occurrence of plaque and gingivitis compared to manual brushing.^{11–13} However, both manual and powered toothbrushes have the ADA Seal of Acceptance, so selection should be based on patient preference.

Dental professionals recommend toothbrushes according to the individual patient’s manual dexterity, oral anatomy, and periodontal health. The toothbrush should be of a size and shape to allow the user to reach every tooth in the mouth. Innovations in head shapes and bristle configurations continue to be introduced in an attempt to improve cleaning contact with tooth and gum line surfaces. Toothbrush firmness is not standardized; toothbrushes designated as soft, medium, or hard may not be comparable across manufacturers. Use of medium- or hard-bristle toothbrushes may result in damage to the tooth enamel and gingival tissue. Softer bristles are more effective at working themselves into crevices and spaces between the teeth, and they are less abrasive on teeth with exposed areas of recession, as well as gentler on soft tissue. Many dental providers and dental hygienists prefer soft, rounded, multitufted, nylon bristle brushes, both because nylon bristles are more durable and easier to clean than natural bristles and because soft, rounded bristle tips are more effective in removing plaque below the gingival margin and on proximal tooth surfaces.

Children’s toothbrushes are smaller than adult toothbrushes and typically are sized by age. Toothbrush size and shape should be individualized according to the size of the child’s mouth. Soft bristles are recommended for children’s

toothbrushes. Children usually can remove plaque more easily with a brush that has short and narrow bristles.

Dental Floss

Plaque accumulation in the interdental spaces contributes to proximal caries and periodontal pocketing. Interdental plaque removal has been reported to reduce gingival inflammation and prevent periodontal disease and dental caries. Dental flossing is the most widely recommended method of removing dental plaque from proximal tooth surfaces that are not adequately cleaned by toothbrushing alone. By removing plaque and debris interproximally, proper flossing also polishes the tooth surfaces and reduces gingival inflammation. Proper flossing technique requires some finger dexterity and practice. If performed improperly, flossing can injure gingival tissue and cause cervical wear on proximal root surfaces. [Table 31–2](#) describes the proper use of dental floss.

TABLE 31–2 Guidelines for Using Dental Floss

- Pull out approximately 18 inches of floss from the dispenser, and wrap most of it around the middle finger.
- Wrap the remaining floss around the same finger of the opposite hand. Approximately an inch of floss should be held between the thumbs and forefingers.
- Do not “snap” the floss down between the teeth; instead, use a gentle, sawing motion to guide the floss up or down to the gum line.
- When the gum line is reached, curve the floss into a C shape against one tooth, and gently slide the floss into the space between the gum and the tooth until you feel resistance.
- Hold the floss tightly against the tooth, and gently scrape the side of the tooth with an up-and-down motion.
- Curve the floss around the adjoining tooth, and repeat the procedure.
- Advance the length of floss to use a new segment for each tooth surface, to avoid the transfer of plaque and bacteria to other teeth.

Floss is a multifilament nylon yarn that is available in waxed or unwaxed form and in various widths, ranging from thin thread to thick tape. Many brands feature product lines of flosses that are coated with additives, such as flavoring, baking soda, or fluoride. In addition, several manufacturers are marketing floss made of materials with superior antishredding properties (e.g., Glide, Oral B Essential).

Product Selection Guidelines. The health care provider should recommend a dental floss product with the ADA Seal of Acceptance.¹⁰ Because there are no differences among various floss types in terms of removing plaque and preventing gingivitis, patient factors (e.g., tightness of tooth contacts, presence of tooth roughness, manual dexterity, personal preference) should be considered in product selection.

Waxed or antishredding floss may be passed between tight-fitting teeth with less shredding and resistance than unwaxed floss. If contacts at the crowns of teeth are too tight to permit interdental flossing, floss threaders can be used to pass floss between the teeth and under the replacement teeth (pontics) of fixed bridges. Floss threaders, available in reusable and disposable forms, usually are thin plastic loops or soft plastic, sewing needle–like appliances. Floss holders have one or two forks that are rigid enough to keep floss taut and a mounting mechanism that allows quick rethreading of floss. Floss picks are small plastic tools with a curved end that holds a piece of dental floss that make flossing with one hand simple. Additionally, the other end of the floss pick can be used to remove large food particles. Products such as these are recommended for patients who lack manual dexterity and for caregivers who assist disabled or hospitalized patients.

American Dental Association (ADA) Seal of Acceptance

ADA evaluates the safety and efficacy of dental products used by dental professionals and the public through its Council on Scientific Affairs' Seal of Acceptance evaluation program. Manufacturers of dentifrices or mouth rinses with therapeutic potential for gingivitis and supragingival dental plaque control may voluntarily submit data to ADA for evaluation. Product labels and promotional material must also comply with ADA standards. The ADA Council on Scientific Affairs allows only products that demonstrate safety and efficacy to support its product category.²⁴

Once a product has earned the ADA seal, it may display that seal for 5 years, provided that it continues to meet all of the requirements.²⁴ The ADA online home page (www.ada.org) provides searchable access to a current listing of dental consumer products that have been awarded the ADA Seal of Acceptance.

Specialty Aids

Cleaning devices that adapt to irregular tooth surfaces better than dental floss are recommended for interproximal cleaning in patients with large interdental spaces. Increased interdental spacing often is characteristic of periodontal disease. The most commonly used aids are tapered triangular wooden toothpicks (Stim-U-Dent) and interdental brushes (Proxabrush). Literature suggests that in addition to regular tooth brushing, interdental brushes may be more effective than flossing; both interdental brushes and flossing reduce plaque better than tooth brushing alone.¹⁴

Oral Irrigating Devices

Oral irrigators, also known as water flossers, work by directing a high-pressure stream of water through a nozzle to the tooth surface. Such devices, however, remove only a minimal amount of plaque from tooth surfaces. Therefore, an irrigating device cannot be viewed as a substitute for a toothbrush, dental floss, or other plaque removal devices, but their use should be considered as an adjunct in maintaining good oral hygiene. These devices are useful for removing loose debris from those areas that cannot be cleaned with a toothbrush (e.g., around orthodontic bands or fixed bridges). Several brands on the market carry the ADA Seal of Acceptance.¹⁰

Oral irrigators also are valuable as vehicles for administering chemotherapeutic agents that inhibit microbial growth in inaccessible regions of the mouth. Patients with advanced periodontal disease should use these devices only under professional supervision, because transient bacteremia may occur after manipulative procedures with the oral irrigator. Oral irrigation devices also are contraindicated in patients who are at risk for the development of bacterial endocarditis.

Pharmacologic Therapy

Chemical Management of Plaque

Chemical management of plaque and calculus can enhance mechanical removal either by acting directly on the plaque bacteria or by disrupting components of plaque to aid in its removal during routine oral hygiene. The use of chemical agents in plaque control may be particularly appropriate for

selected patients who may be unable to brush and floss effectively. Physically or mentally disabled persons (who may not be able to master the manual techniques necessary to brush and floss effectively) and patients with orthodontic appliances (i.e., fixed prostheses) may benefit from adding antiplaque agents to their oral hygiene regimen.

Desirable characteristics for antiplaque agents include the following:

- Selective antibacterial activity; interference with the rate of accumulation or metabolism of supragingival plaque
- Substantivity (sustained retention of the agent in the mouth)
- Compatibility with dentifrice ingredients
- Lack of undesirable adverse effects for the user
- Noninterference with the natural ecology of the normal oral microflora

Use of Fluoride

Fluoride is believed to help prevent dental caries through a combination of effects. When it is incorporated into developing teeth, fluoride acts systemically to reduce the solubility of dental enamel by enhancing the development of a fluoridated hydroxyapatite, which is more resistant to demineralizing acids, at the enamel surface. When applied topically, fluoride facilitates remineralization within early carious lesions during repeated cycles of demineralization and remineralization. Some evidence suggests that fluoride interferes with the bacterial cariogenic process: Fluoride that is chemically bound to organic constituents of plaque may interfere with plaque adherence and may inhibit glycolysis (the process by which sugar is metabolized to produce acid).¹⁵

Fluoridation of the public water supply is an effective and economically sound public health measure that has played a major role in decreasing the incidence of caries.¹⁵ According to the Centers for Disease Control and Prevention, approximately 75% of the U.S. population resides in communities in which the public water supply contains either naturally occurring or added fluoride at optimal levels for decay prevention (1 ppm or 1 mg/L).¹⁶ In addition to reducing dental caries in children, fluoridation has benefits that extend through adulthood, resulting in (1) fewer decayed, missing, or filled teeth; (2) better tooth retention; and (3) a lower incidence of root caries. Current concepts of the action of fluoride relative to its presence in saliva and plaque provide a

rationale for its topical application to prevent caries in all age groups. Most bottled water does not contain fluoride. If manufacturers choose to add fluoride, the U.S. Public Health Service (PHS) recommends limiting the concentration to no more than 0.7 mg/L.¹⁷ This recommendation replaces the previously recommended level of 0.7–1.2 mg/L and aims to promote balance between protection from dental caries, which lead to tooth decay, and the risk of dental fluorosis. The U.S. Food and Drug Administration (FDA), which previously advised manufacturers of bottled water to follow the earlier recommendation, is now proposing a rule to enforce the PHS recommendation.

Mouth rinses and gels that contain sodium fluoride are therapeutic topical applications of fluoride for prevention of dental caries. Use of fluoride mouth rinses enables patients to apply fluoride interproximally. Patients who may benefit from these products include those with fixed orthodontic appliances, those with decreased salivary flow, those at risk for developing root caries, and anyone with difficulty maintaining good oral hygiene. Package directions for fluoride rinses and gels should be followed closely to maximize the safe and effective use of these products. [Table 31–3](#) describes the proper method of applying fluoride treatments.

TABLE 31–3 Guidelines for Using Topical Fluoride Treatments

- Use topical fluoride treatments no more than once a day.
- Brush teeth with a fluoride dentifrice before using a fluoride treatment.
- If using a fluoride rinse, measure the recommended dose (most commonly, 10 mL), and vigorously swish it around the oral cavity, forcing it between the teeth, for 1 minute.
- If using a fluoride gel, brush the gel on the teeth. Allow the gel to remain for 1 minute.
- After 1 minute, spit out the fluoride product. Do not swallow it.
- Do not eat or drink for 30 minutes after the treatment.
- Supervise children receiving fluoride treatments as necessary until they can use the product without supervision.
- Instruct children younger than 12 years in good rinsing habits, to minimize swallowing of the product.

When recommending a nonprescription fluoride mouth rinse, the health care provider should emphasize the need for parents and caregivers to supervise children younger than 12 years as necessary until they are capable of using the

product correctly. Furthermore, children younger than 6 years should avoid these products owing to the increased risk of dental fluorosis, a mottled appearance of the surface enamel of the tooth, if the rinse is repeatedly swallowed.¹⁸ Dental fluorosis can occur when children ingest an excess amount of any fluoride product, particularly for an sufficient period during the time of tooth formation. Although a mild degree of fluorosis is an aesthetic concern, more severe cases can result in pitting and surface defects (see [Color Plates](#), photograph 9). FDA determined that unlike dental caries, mild dental fluorosis does not compromise oral health or tooth function; therefore, the risk of dental caries from inadequate fluoride protection is a greater health hazard than the cosmetic detriment of fluorosis.

Dentifrices

Using dentifrices (e.g., toothpastes) with a toothbrush has been associated with a greater reduction of plaque than that obtained with mechanical brushing alone.¹⁹ Products are marketed as having properties such as caries prevention, plaque reduction, antitartar activity, gingivitis reduction, remineralization induction, cosmetic effect (whitening and stain removal), antisensitivity, or other specialty (e.g., holistic and all natural). Many products may offer multiple such benefits. Dentifrices are available as pastes or gels ([Table 31–4](#)) and commonly contain an abrasive, a surfactant, a humectant (moistening agent), a binder or thickener, a sweetener, flavoring agents, and one or more therapeutic agents (e.g., fluoride) for anticaries activity.

TABLE 31–4 Selected Nonprescription Dentifrices With ADA Seal of Approval							
TABLE 31–4 Selected Nonprescription Dentifrices With ADA Seal of Approval							
Trade Name	Primary Ingredient(s)	Prevent Cavities	Reduce/Prevent Plaque	Reduce/Prevent Gingivitis	Reduce Malodor	Reduce Stains	Sensitivity Control
Arm & Hammer Dental Care Toothpaste	SF 0.24%	✓					
Arm & Hammer Dental Care Toothpaste (with baking soda)	SF 0.24%	✓					
Burt's Bees							
Extra White Burt's Bees Fluoride Extra White	SF 0.243% SF 0.243%	✓ ✓					

Trade Name	Primary Ingredient(s)	Prevent Cavities	Prevent/Reduce Plaque	Prevent/Reduce Gingivitis	Reduce Malodor	Reduce Stains	Sensitivity Control
~~Fluoride~~ Toothpaste							
~~CloSYS~~ ~~CloSYS~~	SF 0.24%	✓			✓		✓
~~Sulfate~~ Free	SF 0.24%	✓			✓		✓
Colgate							
~~Colgate~~ ~~Cavity~~	SMF 0.76%	✓					
~~Protection~~ Protection	SMF 0.76%	✓					
Colgate							
~~Colgate~~ ~~Mint~~	SF 0.24%; StF 0.24%; 0.3% triclosan 0.3%	✓	✓	✓	✓	✓	
~~Mint~~ Crest Tartar							
~~Crest Tartar~~ Protection	SF 0.243% SF 0.243%	✓ ✓					
Crest Pro- ~~Health~~							
~~Advanced~~ ~~Deep Clean~~	SF 0.454 SF 0.454	✓ ✓	✓ ✓	✓ ✓	✓ ✓	✓ ✓	✓ ✓
Deep Clean							
Sensodyne ^a	SF 0.15%; StF 0.35%; potassium nitrate 5%	✓			✓		✓
Sensodyne ^a		✓			✓		✓
Tom's of ~~Maine~~							
~~Maine~~ ~~Whip~~	SF 0.24% SF 0.24%	✓ ✓			✓ ✓	✓ ✓	
White							
Tom's of ~~Maine~~							
~~Whip~~ ~~Cavity~~							
~~Protection~~ ~~Natural~~	SMF 0.76% SMF 0.76%	✓ ✓					
~~Natural~~ ~~Fluoride~~							
~~Toothpaste~~ Toothpaste							

^a Sodium lauryl sulfate free.

^a Sodium lauryl sulfate free.

Key: ADA = American Dental Association; SF = sodium fluoride; SMF = sodium monofluorophosphate; StF = stannous fluoride.

Key: ADA = American Dental Association; SF = sodium fluoride; SMF = sodium monofluorophosphate; StF = stannous fluoride.

Dentifrice abrasives are pharmacologically inactive and insoluble compounds. Common abrasives include silicates, dicalcium phosphate, alumina trihydrate, calcium pyrophosphate, calcium carbonate, and sodium metaphosphate. Dentifrices vary in their degree of abrasiveness; factors such as the size and shape of the abrasive particle, individual brushing technique, and individual salivary characteristics affect the abrasive's potential effectiveness. The ideal abrasive would provide maximal cleaning while causing minimal damage to tooth surfaces. Unfortunately, because of the variability in patients' brushing techniques and oral health status, the ideal dentifrice abrasive does not exist. Low-abrasive dentifrices (including most dentifrice formulations currently marketed in the United States) usually have a low concentration of silica abrasives (10%–25%), whereas high-abrasive dentifrices typically have higher concentrations of the inorganic calcium or aluminum salts previously mentioned (40%–50%). Baking soda, a mild abrasive found in many dentifrices, can prevent caries, reduce plaque, and remove stains and has anti-tartar activity. Studies have demonstrated that toothpastes with baking soda are more effective at removing plaque and stains than toothpastes without it.^{20–22} Sodium lauryl sulfate, present in nearly all toothpastes, does not reduce plaque or gingivitis. It is a chemical used to create a foaming action, which has been implicated as a cause of irritative lesions of the oral mucosa such as aphthous ulcers (i.e., canker sores; see [Chapter 32](#)).²³ Some dentifrices that do not contain sodium lauryl sulfate are listed in [Table 31–4](#).

Fluoride Dentifrices

Fluoride dentifrices are indicated for both preventing and treating carious lesions. In all countries that show a reduction in caries, use of fluoride-containing dentifrices for caries prevention is the norm. All toothpastes with the ADA seal contain fluoride. The most commonly used fluoride sources are sodium fluoride, sodium monofluorophosphate, and stannous fluoride. The first two forms remineralize and strengthen weakened enamel, in addition to reducing gingivitis and sensitivity. In addition to these beneficial effects,

stannous fluoride also creates a protective mineral layer over the teeth to prevent plaque. Patients may experience slight (but noticeable) tooth discoloration after using stannous fluoride dentifrices continuously for 2–3 months. The staining is not permanent and is readily removed at the next professional dental cleaning.

Tartar Control Dentifrices

A number of fluoride dentifrices contain anticalculus compounds for tartar control. Although plaque—not supragingival calculus—is the primary etiologic contributor in marginal periodontal disease, reducing calculus formation remains a goal of good oral hygiene. The ingredients of tartar control dentifrices that prevent or retard new calculus formation are zinc chloride, zinc citrate, and soluble pyrophosphates, which act to inhibit crystal growth. ADA regards the inhibition of supragingival calculus as a nontherapeutic use and therefore does not evaluate anticalculus claims. However, all advertising claims made for accepted products are reviewed for accuracy as described in the box “American Dental Association (ADA) Seal of Acceptance.”²⁴

The use of tartar control toothpastes has been associated with a type of contact dermatitis in the perioral region. The addition of pyrophosphate compounds to these products to increase alkalinity requires increased concentrations of other components for solubilizing (e.g., flavorings, surfactants); presence of such ingredients at high levels is hypothesized to be the cause of irritant contact dermatitis. Patients experiencing such a reaction should be advised to discontinue the tartar control dentifrice and to switch to a non-tartar control fluoride product.

Antiplaque and Antigingivitis Dentifrices

Two toothpastes that are currently accepted by ADA for both antiplaque and antigingivitis indications are Colgate Total, containing triclosan, and Crest Pro-Health, containing stannous fluoride. These dentifrices are not intended for use in children younger than 6 years and 12 years, respectively.¹⁰

Whitening Dentifrices

Although some whitening dentifrices are marketed as strictly cosmetic and do not make any therapeutic claims, numerous products also provide anticaries and gingivitis reduction in addition to effectively removing stains.²⁵ Many

whitening dentifrices, however, contain higher concentrations of abrasives, which are not advised for long-term use or for use by patients with exposed root surfaces. As mentioned previously, toothpastes containing baking soda (e.g., Arm & Hammer Dental Care) have been shown to be effective at stain removal.^{21,25} Other products may contain a pigment (e.g., titanium dioxide, blue covarine) that produces a temporary brightening effect.²⁵ Whitening dentifrices that incorporate oxygenating agents or enzymes rely on a debriding action to remove stained pellicle. Numerous products offer a combination of baking soda and peroxide with fluoride. Whitening dentifrices should not be confused with tooth-bleaching products, as described in the box “A Word About Tooth-Bleaching Products.”

Botanical-Based Dentifrices

Some evidence indicates that nonbotanical-based and botanical-based dentifrices are equally effective at reducing plaque. Reported studies, however, have small sample sizes and were conducted outside of the United States.^{27,28}

Administration Guidelines

Table 31–1 describes the proper method for brushing teeth using a fluoride dentifrice. Children usually are unable to brush by themselves until they are 4 or 5 years of age; to clean their teeth effectively, children may require supervision until 8 or 9 years of age. FDA recommends that caregivers instruct children 6–12 years of age about good brushing and rinsing habits to minimize swallowing of fluoride. All fluoride dentifrice products must contain the following warning on the labeling: “Warning: Keep out of the reach of children under 6 years of age. If you accidentally swallow more than used for brushing, seek professional assistance or contact a poison control center immediately.”

A Word about Tooth-Bleaching Products

The popularity of tooth bleaching has increased in the United States in recent years. Three methods are currently in use: (1) in-office dental bleaching, (2) dental office–supported home bleaching, and (3) nonprescription home bleaching. All three methods use basically the same chemical agents: carbamide peroxide or hydrogen peroxide in

various strengths. The in-office method has the advantage of a one-time treatment, but the stronger bleach and the accelerator light are not necessary to obtain the same result with the dental office-supported home-bleaching process. The latter method involves the use of custom trays. With this process, patients can fine-tune the extent of lightening to personal preference.

The following two nonprescription products (from among many) may aid in lightening teeth:

- Rembrandt Intense Stain Dissolving Strips contain hydrogen peroxide. The kit contains 56 whitening strips that are applied to both upper and lower teeth. Strips dissolve in 5 to 10 minutes, with nothing to remove. The kit is designed for use over a 2-week period.
- Crest 3D WhiteStrips Vivid are translucent film strips impregnated with hydrogen peroxide and other ingredients. The strips are peeled away from a protective backing and then applied by folding them over the 6 upper or lower front teeth (different strips are provided for upper and lower teeth). The teeth will look as though they are covered with small pieces of transparent food wrap. The strips are applied once a day and left in place for 30 minutes. A kit contains enough strips for 10 days.

Product Selection Guidelines

Unless otherwise advised by their dental providers, patients (especially those with periodontal disease, significant gum recession, and/or exposed root surfaces) should choose the least abrasive dentifrice that effectively removes stained pellicle. Although dentifrice abrasives do not pose a risk to dental enamel, toothbrushing action and excessive abrasiveness (which may lead to tooth hypersensitivity) can damage the cementum (the softer material of exposed root surfaces) and dentin.

Extra-strength fluoride dentifrices may be beneficial to patients who have a greater tendency to develop cavities or who reside in an area with non-fluoridated water. Health care providers should recommend a dentifrice that is sodium lauryl sulfate-free for patients with a history of canker sores.

Flavored gel dentifrices disperse rapidly in the mouth and are popular with children. Manufacturers of gel dentifrices have advertised that children brush longer and more thoroughly because of the preferable consistency, translucence, dispersibility, and flavor of these products. This claim has not been substantiated, but many dentifrices marketed for children are of the gel type. Children's products usually have fruit flavors rather than "breath-freshening" minty or cinnamon flavors, which adults prefer.

Mouth Rinses

Regular use of a mouth rinse with plaque or calculus control properties is indicated as an adjunct to proper flossing and toothbrushing with fluoride toothpaste. Antiseptic mouth rinses have demonstrated effectiveness to reduce plaque and gingivitis; however, evidence for the prevention of periodontitis is insufficient.²⁹ Mouth rinse and dentifrice formulations are very similar. As with dentifrices, mouth rinses may be classified as cosmetic or therapeutic ([Table 31-5](#)). Both may contain surfactants, humectants, flavor, coloring, water, and therapeutic ingredients.

TABLE 31-5 Selected Nonprescription Mouth Rinses With ADA Seal of Approval

Trade Name	Primary Ingredient(s)
Fluoride Mouth Rinses	
ACT Anticavity Fluoride Rinse	Sodium fluoride 0.05%
Crest Anticavity Fluoride Rinse	Sodium fluoride 0.022%
Colgate Phos-Flur Ortho Defense	Sodium fluoride 0.044%
Listerine Total Care Anticavity Mouthwash	Sodium fluoride 0.2%
Plaque/Gingivitis Control Mouth Rinses	
Listerine Antiseptic	Thymol 0.064%; eucalyptol 0.92%; methyl salicylate 0.06%; menthol 0.042%
Equate Antiseptic Mouth Rinse	Eucalyptol 0.0.92%; menthol 0.042%; methyl salicylate 0.06%; thymol 0.064%
Cosmetic Mouth Rinses	

Trade Name	Primary Ingredient(s)
CloSYS Alcohol-Free Oral Health Rinse	n/a
TheraBreath Fresh Breath Oral Rinse	n/a

Key: ADA = American Dental Association; n/a = not applicable.

A mouth rinse approximates a diluted liquid dentifrice that does not contain an abrasive. Mouth rinses often contain alcohol, which adds “bite” and freshness, enhances flavor, solubilizes other ingredients, and contributes to the mouth rinse’s cleansing action and antibacterial activity. Flavor contributes pleasant taste and breath-freshening action. Surfactants are foaming agents that aid in the removal of debris. Other active ingredients may include astringents (alum or zinc chloride) that neutralize odoriferous sulfur compounds produced in the oral cavity, demulcents (sorbitol or glycerin) that provide a protective film soothing to oral mucosa, antibacterial agents (cetylpyridinium chloride or thymol), and fluoride.

Cosmetic mouth rinses freshen the breath and clean some debris from the mouth. Mouth rinses can be classified by appearance, flavor, alcohol content, and active ingredients. The most popular cosmetic mouth rinses are medicinal and mint-flavored. Healthy persons normally have some degree of oral malodor, typically on awakening (i.e., “morning breath”). This malodor results from reduced salivary flow, contributing to enhanced bacterial activity and production of odoriferous sulfur compounds, as noted earlier.³⁰ (Other causes of oral malodor in healthy persons are noted later in the “Halitosis” section.) The FDA Advisory Review Panel on Over-the-Counter Oral Health Care Products considers products that are intended to eliminate or suppress mouth odor of local origin in healthy people with healthy mouths to be cosmetics unless they contain antimicrobial or other therapeutic agents.

One important consideration is the potential for breath-freshening mouth rinses to disguise or delay treatment of pathologic conditions that may contribute to lingering oral malodor (e.g., periodontal disease, purulent oral

infections, respiratory infections). If marked breath odor persists after proper toothbrushing, investigation for an underlying cause is warranted; masking the odor with mouth rinse will not address the issue.

Plaque control ingredients include (1) aromatic oils (thymol, eucalyptol, menthol, and methyl salicylate), which are antibacterial and have some local anesthetic activity, and (2) agents with antimicrobial activity (e.g., quaternary ammonium compounds). Listerine, containing the active ingredients thymol, eucalyptol, methyl salicylate, and menthol, was the first mouth rinse to be accepted by ADA as a nonprescription antiplaque/antigingivitis mouth rinse.

Many dental care providers have found anecdotally that use of rinses containing phenol oils, methyl salicylate, and alcohol may bring about a sloughing of the oral epithelium, which subsides when the rinse is discontinued. A similar effect has been observed with the use of lozenges or candies containing cinnamon or other common flavoring substances.

Mouth rinses and gels are generally safe when used as directed, but occasional adverse reactions (e.g., burning sensation, irritation) have been reported. Overuse should be discouraged. Consultation with a health professional is indicated if irritation persists after the patient discontinues use of the product.

Unsupervised use of mouth rinses is contraindicated in patients with mouth irritation or ulceration. These products should be kept out of children's reach. In case of accidental ingestion, the caregiver should seek professional assistance or contact a poison control center.

The alcohol content in mouth rinses ranges from 0% to 27%. Ingestion of alcohol-containing rinses poses a danger for children, who may be attracted by the bright colors and pleasant flavors of these products. Toxicity data concerning children's ingestion of alcohol-containing mouth rinses demonstrate that the amount of alcohol in available mouth rinse preparations is sufficient to cause serious illness and injury. In 2017, more than 1700 cases were reported to poison control centers in which children younger than 12 years of age consumed alcohol-containing mouth washes. Approximately 13% of these cases were categorized as having an outcome of moderate to major health significance.³¹ Responding to concern over the potential danger to children, the Consumer Products Safety Commission issued a final rule that required child-resistant packaging for mouth rinses containing 3 g or more of absolute alcohol per package—the amount that is present in a small quantity

(approximately 2.6 ounces) of a mouth rinse with alcohol 5%. For the purposes of this final rule, the term *mouthwash* includes liquid products that are variously called mouthwashes, mouth rinses, oral antiseptics, gargles, fluoride rinses, antiplaque rinses, and breath fresheners. The rule does not include throat sprays or aerosol breath fresheners. These products should be kept out of children's reach and should not be administered to children younger than 6 years. Labeling includes a warning not to swallow the product but to seek professional assistance or contact a poison control center immediately in case of accidental ingestion.

Complementary and Alternative Therapies

Activated Charcoal

Recently the market has seen a surge of topical oral hygiene products with activated charcoal, particularly those advertising whitening properties. This effect presumably derives from the notable ability of charcoal, with its high surface area, to absorb pigments and stains. Although 96% of commercially marketed products make claims to whiten teeth, data demonstrating this efficacy are very limited, and such claims may rest partly on their novelty.^{32,33}

Probiotics

Because the accumulation of an oral biofilm containing microorganisms results in tooth decay, oral probiotics have been hypothesized to be able to prevent or treat oral diseases like caries, gingivitis, or periodontitis. They exert this action by altering the bacterial biofilm composition and balancing the microflora antimicrobial activity against the effects of pathogenic bacteria. Probiotics may be beneficial in managing periodontal disease such as gingivitis or periodontitis; at present, however, insufficient evidence is available to recommend probiotics for managing dental caries, until more research is conducted.^{34,35}

Vitamin D

Studies have demonstrated that a deficiency in vitamin D can result in low bone mineral density and increased infectious and inflammatory diseases, which has been linked to caries, gingivitis and periodontitis.^{36,37} Vitamin D is vital in the mineralization of bones and teeth, so attaining an optimal vitamin

D level is essential for maintaining oral health. Because this mineralization begins during the fetal period, evidence supports the use of vitamin D supplementation in pregnancy to reduce caries in children.³⁸

Special Population Considerations for Caries Prevention and Plaque Removal

Efforts to reduce childhood caries can begin in infancy, since at birth, the 20 primary teeth that will erupt are present but not visible. Parents should avoid putting the child to bed with a bottle to avoid “baby bottle caries,” which results when the infant is allowed to nurse continuously from a bottle of juice, milk, or sugar water, and should take care to remove plaque and milk residue from the baby’s mouth after each feeding and before bed by wiping the gums with a wet gauze pad. For toddlers, filling training cups with water instead of milk or juice between meals can reduce exposure to cavity-causing bacteria.³⁹

The deciduous teeth usually start to erupt at the age of approximately 6 months and without proper oral care can begin to decay at any time. When the teeth have erupted, a soft, child-size toothbrush can be used for cleaning. ADA recommends that caregivers use a smear (approximately the size of a grain of rice) of fluoride toothpaste for children younger than 3 years and no more than a pea-sized amount of toothpaste for children 3–6 years of age.^{40,41}

In patients with fixed orthodontic appliances, very careful attention to oral hygiene to prevent gingivitis and caries is required because of the ease with which plaque accumulates along the orthodontic brackets. Patients with such appliances need to use a combination of toothbrush types to clean all surfaces effectively. Use of power toothbrushes, oral irrigating devices, floss threaders, and interdental brushes may help remove plaque and debris around orthodontic bands. Orthodontic patients also may want to use a nonprescription fluoride mouth rinse while undergoing treatment.

Patients with removable orthodontic appliances should consult their orthodontist about using a denture cleanser. In addition to manual brushing of orthodontic appliances, some dental care providers recommend a denture cleanser to remove plaque, tartar, odor-causing bacteria, and stain that accumulate on orthodontic appliances.

In patients of advanced age who have natural dentition, topical fluoride

application in the form of a dentifrice, rinse, or gel is indicated to prevent coronal and root caries. Health care providers should continue to recommend fluoride anticaries products to older adult patients. For counseling on oral health care in this age group, review and update of the medication history are essential. Because senior patients are more likely to be taking multiple medications, the incidence of drug-induced or disease-related changes in oral physiology is increased.

No special considerations related to plaque removal have been identified for pregnant or lactating women or for males and females of reproductive age.

Assessment of Caries

When asked to recommend plaque control products, the health care provider should determine what dental care measures the patient is taking, whether these measures meet recommended oral hygiene standards, and how often the patient sees a dental care provider. It also is important to ascertain whether the patient has a history of caries or if the patient suspects that a new carious lesion has developed. Presence of dental caries symptoms—toothache, tooth sensitivity with chewing, or tooth pain with exposure to hot, cold, or sweet foods or beverages—warrants referral to a dental care provider for evaluation and treatment.

Patient Counseling for Caries Prevention

In patient counseling for caries prevention, all explanations of the purposes of various oral hygiene products and the methods for using them should be tailored to the patient's level of understanding. Patients with a history of caries should be encouraged to brush after meals and to consult with a dental provider about the use of topical fluoride products. If caries recurs or is widespread, the patient should be encouraged to visit a dental care provider for treatment. The health care provider should explain the precautions for these products, as well as the possible adverse effects of certain therapeutic ingredients in other products. The box "Patient Education for Prevention of Caries, Gingivitis, and Halitosis" lists specific information for patient counseling on plaque-induced oral disorders.

Beyond these considerations in patient counseling, the health care provider can use the initial clinical encounter to educate the patient about signs and symptoms of oral pathology for which self-care is not adequate or appropriate, as summarized in the box “Exclusions for Self-Treatment for Hygiene-Related Oral Disorders.” The presence of any such exclusion warrants referral of the patient for further evaluation by a primary care provider.

Patient Education for Prevention of Caries, Gingivitis, and Halitosis

The primary objective of self-care for oral hygiene is the removal of plaque to prevent caries, gingivitis, and halitosis. For most patients, carefully following product instructions and the self-care measures listed here will help ensure good oral hygiene.

Nondrug Measures and Other Considerations

- Avoid cariogenic foods, such as foods that contain more than 15% sugar, cling to the teeth, and tend to remain in the mouth after swallowing.
- Eat low-cariogenic-index foods, such as foods that have a high water content (e.g., fresh fruit), stimulate the flow of saliva (e.g., fibrous foods that take longer to chew), or are high in protein (e.g., dairy products).
- To help prevent mouth odor, maintain proper oral hygiene and limit or avoid consumption of foods and products that may cause oral malodor. Also, if you wear dentures, do not wear them while sleeping.
- Note that use of alcohol and tobacco is associated with caries, gingivitis, and halitosis.
- Note that hormonal changes during pregnancy increase the risk of gingivitis.
- Chewing sugarless gum for 20 minutes after meals helps reduce tooth decay as an adjunct to brushing and flossing.

Plaque Removal

Brushing Teeth

- Mechanically remove plaque buildup by brushing teeth at least twice daily with a fluoride dentifrice. (See [Table 31–1](#) for proper brushing technique.)
- Use a brush with soft nylon bristles.
- Replace the brush when the bristles show signs of wear.
- For children younger than 3 years, use a smear (the size of a grain of rice) of fluoride gel once teeth erupt.
- For children 3–6 years of age, apply a pea-sized amount of toothpaste to a child-sized toothbrush, and brush the child's teeth until the child can brush properly.
- Teach children how to rinse the mouth and spit out the toothpaste, to avoid swallowing fluoride.
- Note that tartar control toothpastes have been related to a type of contact dermatitis in the perioral region. If you experience itching or irritation of the mouth after brushing, discontinue the tartar control toothpaste, and switch to a non-tartar control fluoride toothpaste.
- If you are prone to developing caries or gingivitis, consider using a toothpaste with antiplaque or antigingivitis activity. Such toothpastes contain stannous fluoride.
- If you are prone to developing aphthous ulcers, consider using a toothpaste that does not contain sodium lauryl sulfate.

Flossing Teeth

- Floss your teeth at least once a day. (See [Table 31–2](#) for proper flossing technique.)
- Use waxed or Teflon-coated floss for teeth with tight contacts.

Using Mouth Rinses and Gels

- To freshen breath, use a mouth rinse that contains zinc chloride and zinc citrate to eliminate odoriferous volatile sulfur compounds.
- If you are prone to developing caries or gingivitis, consider using a

mouth rinse classified as having antiplaque/antigingivitis activity.

- Note that overuse of mouth rinses containing cetylpyridinium can stain teeth.

Using Topical Fluoride Treatments

- If your drinking water (including bottled water) is not fluoridated, or if you are prone to developing caries, consider using fluoride mouth rinses. (See [Table 31–5](#) for proper use of these products.)
- Supervise children younger than 12 years of age until they are capable of using the product correctly.

Exclusions for Self-Treatment for Hygiene-Related Oral Disorders

- Symptoms of toothache (e.g., pain with or without chewing, localized swelling, hot or cold sensitivity, fever or headache)
- Development of a mottled appearance to the teeth
- Bleeding, swelling, or reddened gums
- Persistent mouth odor despite regular use of fluoride toothpaste, or for which a cause cannot be identified

Gingivitis

Periodontal disease (which may result in tooth loss) affects an estimated 46% of U.S. adults 30 years of age and older.⁴² Similar to statistics for dental caries, the prevalence of periodontal disease is disproportionately higher in Hispanics (63.5%), non-Hispanic blacks (59.1%), and non-Hispanic Asian Americans (50.0%), compared with non-Hispanic whites (40.8%).⁴² Curtailing buildup of plaque can prevent or control this common and significant public health

problem. All forms of periodontal disease are associated with oral hygiene status, not with age. However, as life spans increase and people retain more teeth later in life, both the number of teeth at risk and the susceptible period for development of periodontal disease increase.

Gingivitis, the mildest form of periodontal disease, is a common and reversible inflammation of the gingiva without loss or migration of epithelial attachment to the tooth. Periodontitis occurs when the periodontal ligament attachment and alveolar bone support of the tooth have been compromised or lost (see [Color Plates](#), photographs 10 and 11). Gingivitis may progress to more severe periodontal diseases such as acute necrotizing ulcerative gingivitis and periodontitis, particularly if left untreated.

Pathophysiology of Gingivitis

Gingivitis results from the accumulation of supragingival bacterial plaque. If this accumulation is not controlled, the plaque proliferates and invades subgingival spaces. Although not all gingivitis progresses to periodontitis, the progression from supragingival plaque to gingivitis to periodontitis is well documented, so controlling gingivitis is a reasonable approach to limiting periodontitis.

Other possible etiologic factors include effects of medications such as calcium channel blockers, cyclosporine, and phenytoin. Anticholinergics and antidepressants may cause gingivitis by reducing the flow of saliva. The use of tobacco (both smokeless and smoked) also has been linked to periodontal disease.

Pregnant patients are more susceptible to the development of dental caries and gingivitis. In addition to local factors, varying hormone levels in pregnancy may make gingival tissue more sensitive to bacterial dental plaque. These changes in the connective tissues that make up the periodontium appear to be the primary pathogenic mechanism. Pregnancy gingivitis can be prevented or resolved thorough plaque control. The severity of the inflammatory response and the resulting gingivitis decrease post partum, with a return to pre-pregnancy levels after approximately 1 year.⁴³

Clinical Presentation of Gingivitis

The marginal gingiva (the border of the gingiva surrounding the neck of the tooth) is held firmly to the tooth by a network of collagen fibers.

Microorganisms present in the plaque in the gingival sulcus (the space between the gingiva and the tooth) are capable of producing harmful products (e.g., acids, toxins, enzymes) that damage cellular and intercellular tissue. Early-stage gingivitis signs and symptoms include dilation and proliferation of gingival capillaries, increased flow of gingival fluid, and increased blood flow with resulting erythema of the gingiva. The gingivae themselves also may enlarge, change contour, and appear puffy or swollen as a result of the inflammation (see [Color Plates](#), photograph 10). The inflammatory process of early-stage gingivitis is reversible with effective oral hygiene.

Some common indications that early-stage gingivitis has become chronic gingivitis include changes in gingival color, size, and shape, as well as changes in the ease with which gingival bleeding occurs. Additionally, the flat, knife-edge appearance of the margin of healthy gingiva is replaced by a ragged or rounded edge. Progression usually is slow and insidious—and often painless.

Left untreated, chronic gingivitis may advance to the inflammatory condition of chronic destructive periodontal disease, or periodontitis (see [Color Plates](#), photograph 11). Progression of gingivitis may parallel an increase in the proportion of bacterial species implicated in the genesis of periodontitis.

Prevention of Gingivitis

Because prevention of gingivitis depends on calculus prevention and plaque control, the same measures described for prevention of caries pertain to gingivitis. Active ingredients that prevent gingivitis and are commonly found in dentifrices, mouth rinses, and other antiplaque products include triclosan, cetylpyridinium chloride, and stabilized stannous fluoride. Brushing and flossing can cure early gingivitis that arises from irritating food debris and plaque. The most important factors in reversing gingivitis and in preventing and controlling periodontal disease are adequate removal and control of supragingival plaque. Patients who notice signs of early gingivitis such as

bleeding gums during tooth brushing should be referred to a dental care provider.

Special Population Considerations for Gingivitis

In general, self-care for prevention of gingivitis requires no specific considerations for the following patient populations: children, pregnant or lactating women, males and females of reproductive age, and older adults.

Assessment of Gingivitis

Before recommending oral hygiene products, the health care provider should evaluate the patient's oral hygiene regimen. An important issue is whether the patient has a history of gingivitis or current signs and symptoms of gingivitis, as well as what preventive measures the patient has tried or is using. Checking the medical and medication histories will identify asymptomatic patients who are at risk for gingivitis. Any signs or symptoms of gingivitis—swollen gums, gums that bleed with brushing or flossing, receding gums, or gums that appear darker red than usual—warrant referral to a dental care provider for evaluation and treatment.

The health care provider should be cognizant of the association between pregnancy and gingivitis and should address this potential issue during counseling on prescription prenatal vitamins. Besides monitoring the pregnant patient's medications for safety, the provider has an opportunity to encourage the patient to have a dental checkup and to stress the importance of careful attention to brushing and flossing to avoid oral health problems.

Patient Counseling for Gingivitis

Because gingivitis is not usually associated with pain, patients are unlikely to seek dental care for this problem alone. A more likely scenario is patient-initiated contact with a health care provider to request oral hygiene information and product recommendations. In such encounters, it may be appropriate to suggest specific oral hygiene methods and emphasize possible adverse effects of certain products. Case 31-1 provides an example of

assessment of a patient with gingivitis. The box “Patient Education for Prevention of Caries, Gingivitis, and Halitosis” lists specific information for patient counseling.

The health care provider should also use such clinical encounters as an opportunity to warn patients with suspected gingivitis that the disease is a serious problem warranting professional attention. Counseling should emphasize that adherence to an oral hygiene program is vital to preventing gingivitis.

Considerations in pregnant patients are reviewed under “Assessment of Gingivitis.”

Case 31–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient has had red, slightly swollen gums for the past 3 weeks.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	She experienced a “little bit of bleeding” at her dental cleaning visit 2 days ago.
c. Description of the patient's efforts to relieve the symptoms	Patient brushes her teeth twice daily.
d. Patient's identity	Katherine Stonesifer
e. Patient's age, gender, height, and weight	42 years, female, 5 ft 3 in., 155 lb
f. Patient's occupation	School teacher

Relevant Evaluation Criteria	Scenario/Model Outcome
g. Patient's dietary habits	Normal, healthy diet
h. Patient's sleep habits	6–8 hours of sleep each night
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Patient has hypothyroidism and takes levothyroxine 125 mcg PO daily.
j. Allergies	None
k. History of other adverse reactions to medications	None
l. Other (describe) _____	Ms. Stonesifer's dentist referred her to your pharmacy for dental hygiene products.
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	The patient appears to have gingivitis.
3. Identify exclusions for self-treatment.	Although Ms. Stonesifer had red, swollen gums and bleeding at her dental cleaning, which are exclusions for self-care (see the box "Patient Education for Prevention of Caries, Gingivitis, and Halitosis"), she was recently seen by a dental care provider (i.e., she was not avoiding treatment), who referred her to you. You can recommend self-care.
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer Ms. Stonesifer to a dental care provider. (2) Recommend self-care with a mouth rinse and floss with education about proper oral care. (3) Recommend self-care until Ms. Stonesifer can see a dental care provider.

Relevant Evaluation Criteria	Scenario/Model Outcome
	(4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Recommend self-care with a mouth rinse and flossing, with education about proper oral care.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Regular use of a plaque/gingivitis mouth rinse and flossing, in addition to brushing your teeth, will improve your oral health with a decrease in your symptoms."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"A plaque/gingivitis mouth rinse has ingredients that some other mouth rinses do not have to treat your symptoms. It is important to select one that has the American Dental Association Seal of Acceptance. Regular flossing helps prevent plaque from depositing in hard-to-reach places between your teeth, which can lead to inflamed gums."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
a. Appropriate dose and frequency of administration	"Use a plaque/gingivitis mouth rinse such as Listerine Antiseptic once daily and waxed floss once daily."
b. Maximum number of days the therapy should be employed	n/a
c. Product administration procedures	See Tables 31-2 and 31-3 .
e. Most common adverse effects	"You may experience a little burning from the mouth wash. Your gums may bleed with flossing for the first few days."
f. Adverse effects that warrant	"If your gums bleed with flossing for more than a few

Relevant Evaluation Criteria	Scenario/Model Outcome
medical intervention should they occur	days or you have bleeding that won't stop, see your dental care provider."
g. Patient options in the event that condition worsens or persists	"See your dental care provider for further evaluation."
h. Product storage requirements	Store at room temperature.
i. Specific nondrug measures	"Continue to brush your teeth twice daily."
Solicit follow-up questions from the patient or caregiver.	"Should I change my manual toothbrush to a powered one?"
Answer the patient's or caregiver's questions.	"There is some evidence that powered toothbrushes reduce plaque and gingivitis better than manual brushing, so you could switch to a powered toothbrush."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Call Ms. Stonesifer in 1 week to evaluate her response to your recommendations.

Key: n/a = Not applicable.

Halitosis

A recent meta-analysis estimated that halitosis, or oral malodor (usually known as bad breath), affects greater than 31.8% of the population worldwide.⁴⁴

Pathophysiology of Halitosis

Causes of halitosis may be related to both systemic and oral conditions; in a majority of cases, however, the etiology involves oral pathology (e.g. dental caries, periodontal disease, oral infections, mucosal ulcerations, tongue

coating, impacted food or debris).⁴⁵

Medications that have anticholinergic properties often cause xerostomia, which also can lead to mouth odor. Many foods and products such as garlic, tobacco, onions, alcohol, and other substances may contribute to mouth odor as well.

Most foul breath odors arise from volatile sulfur compounds (VSCs), which can be produced by breakdown of food debris left in the mouth or in systemic conditions in which VSCs are eliminated in exhaled air.

Prevention of Halitosis

Prevention of halitosis relies on the removal of plaque and the prevention of calculus formation as described for prevention of caries. One of the primary sites for the formation of VSCs is the back of the tongue. Plaque and VSCs in this area of the mouth can seed the tonsillar crypts with malodorous debris. Brushing both the teeth and tongue is helpful, but some dental care providers have found that the use of a tongue-cleaning device (e.g., a tongue blade) may be the best way to clean the circumvallate papillae area of the tongue. Cleaning this posterior dorsal area not only will remove the VSCs but also will prevent them from spreading to the tonsils.

Zinc salts and chlorine dioxide are most effective in the chemical prevention of oral malodor. Zinc salts reduce the receptor binding necessary for VSC production and kill gram-negative bacteria. Chlorine dioxide breaks disulfide bonds and oxidizes the precursors of VSCs.

Any patient who complains of severe or lingering halitosis without a readily identifiable cause (e.g., smoking) should be advised to see a dental care provider for a thorough evaluation. Masking foul taste and odor with cosmetic mouth rinses may delay necessary dental or medical assessment and any needed treatment.

Special Population Considerations for Halitosis

No self-care considerations related to prevention of halitosis have been identified for the following patient populations: children, pregnant or lactating

women, males and females of reproductive age, and older adults.

Assessment of Halitosis

When assessing a patient for halitosis, the health care provider should evaluate the patient's dental hygiene. Ideally, both medication and medical histories are obtained to help identify the cause of the halitosis, as discussed in the "Pathophysiology of Halitosis" section (see also "Xerostomia" in [Chapter 32](#)). Patients with medical conditions associated with halitosis and those with halitosis that persists despite proper dental hygiene should be referred to their dental care provider for evaluation and treatment.

Patient Counseling for Halitosis

For patients with mouth odor related to poor dental hygiene, the health care provider should reinforce proper techniques for maintaining dental hygiene to prevent tooth and gum problems, including brushing and flossing, and should recommend appropriate products, with explanations of their use. The box "Patient Education for Prevention of Caries, Gingivitis, and Halitosis" lists specific information for patient counseling on prevention of halitosis.

Hygiene-Related Denture Problems

Pain along the gingival ridge under a denture prosthesis suggests the presence of *denture stomatitis* or a related condition. Denture stomatitis, an inflammation of the oral tissue in contact with a removable denture, results from poor cleaning of dentures and can lead to chronic candidiasis.⁴⁶

Pathophysiology of Hygiene-Related Denture Problems

Dentures accumulate plaque, stain, and calculus by a process very similar to that occurring on natural teeth. Contact of the denture plaque mass with oral

tissues leads to predictable toxic results. Poor denture hygiene contributes to fungal and bacterial growth that not only affects the patient aesthetically (with unpleasant odors and staining) but also seriously compromises the patient's oral health (from inflammation and mucosal disease) and ability to wear the dentures successfully.

Chronic atrophic candidiasis is common in patients with full or partial dentures. This condition may be attributed to infection with *Candida* organisms, which is more prevalent among denture wearers.⁴⁶ On inspection, the inflamed denture-bearing area may appear granular or erythematous and edematous, associated with soreness or a burning sensation (see [Color Plates](#), photograph 12). Inflammation secondary to *Candida* infection is generalized, involving the entire denture-bearing tissue area, whereas inflammation secondary to the trauma of ill-fitting dentures usually is localized to the specific area of the trauma. Failure to remove the denture at bedtime and to clean it regularly will worsen this condition.

Angular cheilitis (soreness and cracking at the corners of the mouth) is commonly associated with chronic atrophic candidiasis, other forms of oral candidiasis, and poor denture fit. The cheilitis lesions often can be treated effectively with terbinafine cream. If a staphylococcal organism also is involved, a prescription from the patient's primary care provider will be needed.

Prevention of Hygiene-Related Denture Problems

Removing plaque from dentures helps prevent gum infections, staining of dentures, and mouth odor. Specialty brushes and aids are available to remove plaque from hard-to-clean areas on fixed orthodontic appliances (e.g., spaces around a bridge, implant, or orthodontic band) and dentures. Dentures should be cleaned thoroughly at least once daily to remove unsightly stains, debris, and plaque. Abrasive and chemical cleansers formulated specifically for dentures are available ([Table 31–6](#)). A combination regimen of brushing dentures with an abrasive cleaner and soaking them in a commercial cleaning solution is recommended.

TABLE 31-6 Selected Nonprescription Denture Products

Denture Adhesive
Adhesadent Denture Adhesive Cream
Denture Cleaners
Cleanadent Cleansing Paste
Efferdent Denture Cleanser Tabs
Fresh 'N Brite Denture Cleaning Paste

Denture cleansers for brushing, in either a paste or powder formulation, contain mild abrasives (e.g., calcium carbonate) and must be applied properly with specialty brushes adapted to the denture's contour to remove stains, plaque, and calculus. Overly vigorous scrubbing can abrade the denture's acrylic materials and deform the metal clasps. To prevent irritation of oral tissues, the patient should thoroughly rinse the abrasive cleaner from the denture. After initial brushing, the denture should be soaked in a cleansing solution (alkaline peroxide, hypochlorite, or dilute acids) to help remove remaining plaque and bacteria. Brushing the denture after it has soaked further enhances plaque removal.

Alkaline peroxide products are the most commonly used chemical denture-soaking cleansers. These powders or tablets are dissolved in water to become alkaline solutions of hydrogen peroxide, causing oxygen to be released for a mechanical cleaning effect. These products are most effective on new plaque and stains when the denture is soaked for 4 to 8 hours. The alkaline peroxides have few serious disadvantages and do not damage the surface of acrylic resins.

Sodium hypochlorite (bleach) removes stains, dissolves mucin, and is both bactericidal and fungicidal. *Denture plaque* consists of cells embedded in a matrix that serves as a surface on which calculus may develop. Hypochlorite cleansers act directly on the organic plaque matrix to dissolve its structure, but they cannot dissolve calculus once it has formed. The most serious drawback with any hypochlorite product is that the bleach corrodes metal denture

components (e.g., the framework and clasps of removable partial dentures, solder joints, and possibly the pins holding the teeth). The addition of anticorrosive phosphate compounds has greatly reduced this problem, but these products should be used for only 10-minute soaks (to limit exposure) and not more often than once a week.

Acid-containing soaking solutions also can be corrosive to metals, so short soaking times are recommended with use of these solutions. A sonic or ultrasonic cleaning device, when used with a commercially prepared solution, is easy to operate and cleans more effectively than soaking alone. However, some hand brushing may still be required.

All denture-cleansing products should be rinsed off the denture completely before it is inserted into the mouth, to reduce tissue irritation. All denture cleansers should be kept out of children's reach because of the potential for eye or skin irritation, and because they are toxic if accidentally ingested. Stains that are resistant to proper denture brushing and soaking in available solutions should be evaluated by a dental care provider.

Only products that are specifically formulated for denture cleansing should be used. Household cleansers (sometimes used by patients for soaking dentures) are not appropriate and may be ineffective or may damage the denture material. The use of whitening toothpastes (which are formulated for use with natural dentition) should be discouraged as well, because they are too abrasive to be used safely on denture material.

Patients should not soak or clean dentures in hot water or hot soaking solutions, because distortion or warping may occur.

Patients of advanced age or disabled persons may prefer an alkaline peroxide soak solution for daily, overnight cleaning. Unlike alkaline hypochlorite and acid cleansers, alkaline peroxide cleansers do not corrode metal components of dentures.

Assessment of Hygiene-Related Denture Problems

Before recommending any type of oral hygiene product, the health care

provider should identify what denture care measures the patient is taking and assess whether those measures are adequate for oral health and successful wear of dentures or other appliance. Another important aspect of the initial assessment is to determine whether the patient suffers from denture stomatitis or inflammation secondary to ill-fitting dentures, necessitating referral to a dental care provider for evaluation and treatment. Case 31–2 illustrates assessment of a patient with a hygiene-related denture problem.

Case 31–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient is complaining of gum inflammation and soreness in the back upper right area of his mouth. He also noticed some white patches on his tongue.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Symptoms are worse when he wears his dentures overnight. They decrease somewhat when he soaks them in a cleaner overnight.
c. Description of the patient's efforts to relieve the symptoms	He removes the dentures when the sore area gets really uncomfortable, but he can't always do this, especially in public.
d. Patient's identity	George Clancy
e. Patient's age, gender, height, and weight	64 years, male, 6 ft 1 in., 210 lb
f. Patient's occupation	Retired mailman
g. Patient's dietary habits	Normal healthy diet
h. Patient's sleep habits	Averages 6 hours per night and takes a 1-hour nap every afternoon.
i. Concurrent medical conditions,	<i>High blood pressure:</i> amlodipine 10 mg, 1 tablet

Relevant Evaluation Criteria	Scenario/Model Outcome
prescription and nonprescription medications, and dietary supplements	daily; hydrochlorothiazide 25 mg, 1 tablet daily
	<i>High cholesterol:</i> simvastatin 40 mg, 1 tablet daily
j. Allergies	Sulfa
k. History of other adverse reactions to medications	Oxycodone/APAP: upset stomach
l. Other (describe) _____	n/a
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Mr. Clancy has denture stomatitis and possible <i>Candida</i> infection.
3. Identify exclusions for self-treatment.	Symptoms of denture stomatitis and signs of infection (white patches on tongue)
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer Mr. Clancy to a dental care provider. (2) Recommend appropriate self-care with a denture dentifrice. (3) Recommend self-care until Mr. Clancy can see a dental care provider. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Refer Mr. Clancy to a dental care provider. Educate him about denture care: His dentures should be thoroughly cleaned with a denture brush and denture paste daily. Then they should be soaked in a dental cleanser solution. He also should remove his dentures every evening.

Relevant Evaluation Criteria	Scenario/Model Outcome
6. Describe the recommended therapeutic approach to the patient or caregiver.	"You will need to see a dental health care provider for your symptoms."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"This option is best because you may have an infection that requires an antifungal medication to be prescribed."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	"Proper denture hygiene is important to prevent this condition in the future. Brush your dentures using a denture brush and denture paste daily. Then soak the dentures in a dental cleanser. Be sure to remove your dentures every evening."
Solicit follow-up questions from the patient or caregiver.	"Can I use whitening toothpaste to remove stains on my dentures?"
Answer the patient's or caregiver's questions.	"No. Only products that are specifically formulated for denture cleansing should be used. Whitening toothpastes are too abrasive to use on dentures."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Mr. Clancy within 1 or 2 days to make sure he made an appointment and sought dental care.

Key: APAP = Acetaminophen; n/a = not applicable.

Patient Education for Hygiene-Related Denture Problems

The objective of self-care is to prevent bacterial or fungal infections of the mouth by removing plaque from the dentures. For most patients, carefully following product instructions and the self-care measures listed here will help ensure good denture hygiene.

- Thoroughly clean dentures at least once daily to remove unsightly stain, debris, and potentially harmful plaque.
- Preferably, brush dentures with an abrasive cleaner using a brush designed to adapt to the dentures contour, and then soak them in a chemical cleanser. This combination regimen is more effective in removing plaque and bacteria.
- Do not scrub the denture surface vigorously; this action can abrade the acrylic materials and deform the metal clasps.
- If using sodium hypochlorite or acid-containing cleansers, limit soaking to 10 minutes to avoid corrosion of metal denture components.
- To prevent irritation of oral tissues, thoroughly rinse the dentures after using an abrasive cleaner or chemical cleanser.
- Keep all denture cleansers out of children's reach. These agents can cause eye or skin irritation or toxicity if accidentally ingested.
- Do not use household cleansers or whitening toothpastes to clean dentures. These agents may damage denture material.
- Do not soak or clean dentures in hot water or hot soaking solutions. Distortion or warping of the denture may occur.
- Do not sleep while wearing your dentures. Decreased levels of saliva during sleep may contribute to plaque buildup on the denture.

Patient Counseling for Hygiene-Related Denture Problems

Denture wearers may tend to blame their appliances for any oral discomfort, rather than their hygiene regimen. The health care provider should emphasize that diligent plaque removal from dentures is the key to preventing denture stomatitis. The methods of cleaning dentures, including their advantages and

disadvantages, should be explained. The health care provider should recommend a denture cleanser that accommodates the patient's preferences and should reinforce the methods of use. The box "Patient Education for Hygiene-Related Denture Problems" lists specific information for patient counseling.

Key Points for Prevention of Hygiene-Related Oral Disorders

- Removing plaque and modifying the diet are the main goals of self-care to prevent caries, gingivitis, and halitosis.
- Mechanical removal of plaque by brushing and flossing is essential for good oral health.
- Mouth rinses may augment the benefits of brushing and flossing procedures and may be used to freshen breath or as antiplaque or antigingivitis adjuncts.
- Topical fluorides may be used in patients with high caries activity.
- Parents must supervise oral hygiene measures in children younger than 12 years as necessary until they can use the products without supervision.
- Denture cleaners may be used to remove debris physically and to prevent bacterial and/or fungal infections.
- If a patient has specific problems related to the purpose or use of these products, consultation with a dental care provider should be recommended.

Chapter 32: Orofacial Pain and Discomfort

Authors: Nicole Paolini Albanese, Mark Donaldson

Tooth Hypersensitivity

Tooth hypersensitivity, or dentin hypersensitivity, is one of the orofacial pain and discomfort ailments that can occur throughout the human life span.¹ This disorder is characterized by a short, sharp pain arising from exposed dentin (i.e., mineralized tissue of teeth internal to crown enamel and root cementum) in response to a stimulus—thermal, chemical, or physical—that cannot be ascribed to any other form of dental defect or disease.^{2–5} Tooth hypersensitivity affects 10%–30% of the adult population, with increased incidence between the ages of 20 and 50 years.^{3,5} Some investigators suggest that the first premolars and canines are the teeth most commonly affected, in keeping with their prominent position in the maxillary and mandibular arches.³

Pathophysiology of Tooth Hypersensitivity

Two processes are required for the development of dentin hypersensitivity: (1) Dentin must become exposed through loss of enamel or gingival recession (lesion localization, facial piercings), and (2) the dentin tubules must be open to both the oral cavity and the pulp (lesion initiation).^{2–4} The roots of teeth are usually covered by gum tissue (gingiva), but infection (e.g., periodontal disease) or injury² (e.g., aggressive or improper brushing) can cause the gums to recede. The cementum covering affected root surfaces may be reduced by further injury (attrition, abrasion, or erosion), eventually exposing the underlying porous dentin. When stimuli such as heat, cold, pressure, or acid touch exposed dentin or reach an open tubule, fluid flow in the dentin tubule is increased, and the underlying nerves are stimulated, resulting in pain.^{2–4,6}

Enamel, which covers the anatomic crowns of the teeth and is the most densely mineralized body tissue, is resistant to abrasion by normal toothbrushing. Consistent clinical data correlating brushing habits and dentin hypersensitivity are lacking, with an array of conflicting opinions, although overly aggressive brushing may be a contributing factor.^{2,6,7} Clark and Levin

define aggressive brushing as the use of excessive force with a hard-bristled toothbrush.³ However, a clear association between diet and resulting hypersensitivity is recognized. The intake of acidic foods and beverages is correlated with effect on the basis of duration of exposure, rather than frequency of use. In other words, taking a long time to eat or drink an acidic food causes more damage than the frequency of eating or drinking the acidic food.⁶ Tooth hypersensitivity is more common in persons with periodontitis or after procedures such as deep scaling, root planing, orthodontic tooth movement, or periodontal (gum) surgery.^{2,3,6} Tooth whitening procedures, whether done at home or by a trained clinician, also can cause dentin sensitivity.

Clinical Presentation of Tooth Hypersensitivity

The patient with tooth hypersensitivity experiences pain from hot, cold, sweet, or sour solutions, as well as when hot or cold air touches the teeth. As individual pain thresholds vary, so does the pain experienced from tooth hypersensitivity. Pain varies in intensity, ranging from mild discomfort to sharp, excruciating pain. Although tooth hypersensitivity is self-treatable, toothache is not; therefore, it is critical to differentiate between these two conditions (Table 32–1). Resolution of pain associated with toothache, fractured dentition, ill-fitting dentures, or suspected infection (abscess) requires professional dental care. Only a dentist can adequately evaluate and treat these conditions; therefore, the affected patient should see a dentist without delay.

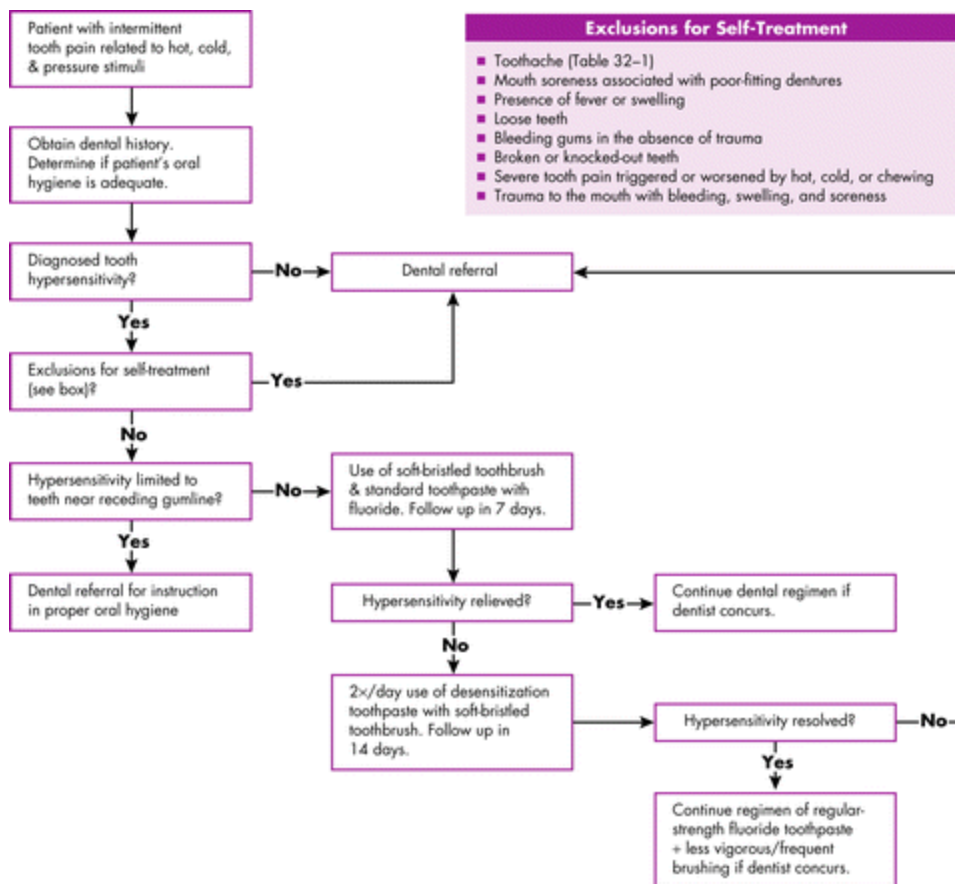
TABLE 32–1 Differentiation of Tooth Hypersensitivity and Toothache

Feature	Tooth Hypersensitivity	Toothache
Etiologic mechanism	Exposed and open dentin tubules	Bacterial invasion extending to the pulp
Pathophysiology	Stimuli (heat, cold, pressure, acid) cause fluid in the dentinal tubules to expand and shrink, stimulating pulp nerve fibers and resulting in pain.	Inflammatory response to invading bacteria stimulates free nerve endings in the pulp.

Feature	Tooth Hypersensitivity	Toothache
Causes	Attrition, abrasion, erosion, tooth/restoration fracture, faulty restoration, or gingival recession	Cavitation/decay present in tooth/teeth under existing restoration, tooth/restoration fracture, or trauma to the dentition
Symptoms	A quick, fleeting, sharp, or stabbing pain on exposure to thermal, chemical, or physical stimuli, which stops after stimuli are no longer present	Pain that remains even in the absence of stimulus; intermittent, short, and sharp pain on stimulation may indicate reversible damage; continuous, dull, and throbbing pain without stimulation usually indicates irreversible damage.
Assessment	Hypersensitivity due to attrition, abrasion, or erosion is not serious and is self-treatable; sensitivity due to fracture, faulty restoration, or gingival recession warrants referral to a dentist.	Requires dental care for resolution

Source: References [2–9](#).

Algorithm: Tooth Hypersensitivity



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FIGURE 32-1 Self-care for tooth hypersensitivity. (Source: References 2-9.)

Treatment of Tooth Hypersensitivity

Treatment Goals

The goals of self-treating tooth hypersensitivity are (1) to repair the damaged tooth surface using an appropriate toothpaste and (2) to replace aggressive or improper toothbrushing practices with optimal technique. When these goals have been achieved, tooth hypersensitivity may be eliminated.

General Treatment Approach

Pain related to tooth hypersensitivity can be challenging. Acute pain may

cause anxiety, and the patient may not seek care from a dentist but rather will try to self-treat with the aid of a pharmacist.² Before recommending self-treatment for tooth pain, the health care provider should determine if the patient is a candidate for self-care. [Figure 32–1](#) outlines self-treatment for tooth hypersensitivity and lists exclusions for self-care.^{2–8}

Nonpharmacologic Therapy

Treatment plans for tooth hypersensitivity should include identification and elimination of predisposing factors, such as acid exposure and potentially improper or aggressive toothbrushing technique. Brushing teeth within 30–60 minutes of consuming acidic foods or drinks should be avoided, to reduce the effects of acids and abrasions. If correct brushing techniques with a fluoride toothpaste do not result in improvement, a desensitizing dentifrice containing either stannous fluoride, sodium fluoride, or sodium monofluorophosphate or a low-abrasion toothpaste should be used ([Table 32–2](#)). For this purpose, a 1-inch strip of a desensitizing toothpaste with fluoride is applied to a soft-bristle toothbrush, followed by brushing as usual. Dentin permeability can be increased after ingestion of acidic foods or beverages.^{2,6} Fluoride is discussed in further detail in [Chapter 31](#).

TABLE 32–2 Selected Nonprescription Desensitizing Toothpastes	
Trade Name	Primary Ingredient(s)
Colgate Sensitive Multiprotection	Potassium nitrate 5%; sodium fluoride 0.24%
Colgate Sensitive Pro-Relief	Arginine 8%
Colgate Sensitive Pro-Relief Original	Potassium nitrate 5%; sodium fluoride 0.24%
Colgate Sensitive Pro-Relief Enamel Repair	Potassium nitrate 5%; sodium monofluorophosphate 1.14%
Colgate Sensitive Pro-Relief Whitening	Potassium nitrate 5%; sodium fluoride 0.24%
Colgate Total Zx Pro-Shield Plus Sensitivity	Potassium nitrate 0.24%; sodium monofluoride 0.055%; zinc citrate trihydrate 0.096%
Colgate Total Whole Mouth	Stannous fluoride 0.454%

Trade Name	Primary Ingredient(s)
Health	
Crest Pro-Health ^a	Stannous fluoride 0.454%
Crest Pro-Health Whitening ^a	Stannous fluoride 0.454%
Crest Gum and Sensitivity, Gentle Whitening	Stannous fluoride 0.454%
Crest 3D White	Potassium nitrate 5%; sodium fluoride 0.243%
Sensodyne Fresh Impact ^a	Potassium nitrate 5%; sodium fluoride 0.15%
Sensodyne Maximum Strength with Fluoride	Potassium nitrate 5%; sodium fluoride 0.15%
Sensodyne ProNamel	Potassium nitrate 5%; sodium fluoride 0.15%
Tom's of Maine Sensitive	Potassium nitrate 5%; sodium fluoride 0.24%
Tom's of Maine Whole Care	Sodium monofluorophosphate 0.76%

^a Carries the American Dental Association (ADA) Seal of Acceptance.

Pharmacologic Therapy

In general, two pharmacologic mechanisms have been recruited for the treatment of tooth hypersensitivity. The first mechanism involves depolarizing the excited nerves in the tubules and pulp to disrupt the pain stimulus neuronal response.^{2,3,6} A potassium salt, usually potassium nitrate, diffuses along the dentin tubules to decrease the excitability of intradental nerves and alter its membrane potential. The potassium nitrate acts on the dentin to block the perception of stimuli that patients with healthy teeth usually do not experience. The second mechanism involves minimizing the flow of fluid by sealing the exposed dentin.^{2,3,6} A fairly recent technology using 8% arginine, an amino acid naturally found in saliva, combined with calcium carbonate, works by occluding the exposed dentinal tubules.^{2,3,6} This treatment prevents the fluid from moving into the tubules, which is the cause of hypersensitivity. Both of these mechanisms have been implemented in the design and manufacture of desensitizing dentifrices. **Table 32–2** lists selected desensitizing toothpastes

and their active ingredients.

Potassium nitrate 5% is the most widely used and generally accepted ingredient in products for decreasing tooth sensitivity. Most commercially available desensitizing dentifrices are combination products containing potassium nitrate and sodium fluoride, in various concentrations. Some studies have demonstrated that patients with tooth sensitivity experience a reduction in their symptoms after using a potassium nitrate-containing dentifrice for just 2 weeks.^{3,7}

Additionally, products containing arginine and calcium carbonate or calcium sodium phosphosilicate also have been found to be efficacious for the treatment of tooth sensitivity.^{2-4,6} Clinically important drug interactions for desensitizing toothpastes are listed in [Table 32-3](#). Patients consuming calcium-containing products need to be aware that the excess calcium can affect the bioavailability of fluoride. This potential adverse interaction should be emphasized by the oral healthcare practitioner (OHCP) and pharmacist during counseling before initiation of fluoride-containing products.

TABLE 32-3 Clinically Important Drug-Drug Interactions With Nonprescription Orofacial Pain and Discomfort Agents

Active Ingredient	Interacting Drug	Potential Interaction	Management/ Preventive Measures
Desensitizing Toothpastes			
Potassium nitrate	ACEIs, ARBs, potassium- sparing diuretics	These agents increase the risk for development of hyperkalemia.	Be cautious with this combination.
Sodium fluoride	Calcium-rich foods	Foods rich in calcium can decrease the bioavailability of fluoride by up to 25%.	Avoid concurrent use if possible.
Stannous fluoride	Calcium	Calcium can form insoluble compounds with fluoride and reduce absorption by 10%-25%.	Avoid concurrent use if possible.
Oral Debriding and Wound-Cleansing Agents			

Active Ingredient	Interacting Drug	Potential Interaction	Management/ Preventive Measures
Carbamide peroxide	No drug interactions with topical carbamide peroxide have been reported.		
Hydrogen peroxide	No drug interactions with topical hydrogen peroxide have been reported.		
Topical Oral Anesthetics			
Benzocaine	Concurrent use of other drugs that can cause methemoglobin formation, such as prilocaine, nitrates, or sulfonamides	Rare and sometimes fatal cases of methemoglobinemia have been reported with the use of topical or oromucosal benzocaine products.	Avoid concurrent use.
Camphor	Hepatotoxic herbs and supplements	Theoretically, concomitant use of camphor with other potentially hepatotoxic herbs and supplements may increase the risk of developing liver damage.	Avoid concurrent use with androstenedione, chaparral, comfrey, DHEA, germander, kava, niacin, pennyroyal oil, red yeast, and others if possible.
Herpicin-L Lip Balm	No drug or herbal interactions with any of the individual ingredients comprising topical Herpicin-L Lip Balm have been reported.		
Topical Oral Protectants			
Menthol	No drug interactions with topical menthol have been reported.		
Glycyrrhiza (licorice) extract	Antihypertensive medications	Theoretically, licorice may reduce the effect of antihypertensive drug therapy because it is recognized to increase blood pressure in a dose-dependent manner.	Avoid concurrent use if possible.
	Warfarin	Licorice seems to increase metabolism	Avoid concurrent use.

Active Ingredient	Interacting Drug	Potential Interaction	Management/ Preventive Measures
		and decrease levels of warfarin, probably by induction of CYP2C9 metabolism.	
	CYP3A4 substrates (lovastatin, clarithromycin, cyclosporine, diltiazem, estrogens, indinavir, triazolam, numerous others)	Licorice appears to induce CYP3A4 metabolism.	Avoid concurrent use if possible.
Oral Rinses			
Eucalyptol	Antidiabetic medications	Preliminary research suggests eucalyptus may have hypoglycemic activity and may have additive effects when used with antidiabetes medications.	Avoid concurrent use if possible and monitor blood glucose levels closely.
Bee Propolis	Anticoagulant and antiplatelet medications	In vitro evidence suggests that the propolis constituent caffeic acid phenethyl ester can inhibit platelet aggregation.	Avoid concurrent use if possible.
Topical Treatments			
Docosanol	No drug or herbal interactions with topical docosanol have been reported.		
Saliva Substitutes and Other Xerostomia Products			
Isomalt	No drug or herbal interactions with isomalt have been reported.		
Xylitol	No drug or herbal interactions with xylitol have been reported.		

Active Ingredient	Interacting Drug	Potential Interaction	Management/ Preventive Measures
Glucose oxidase	No drug or herbal interactions with glucose oxidase have been reported.		
Sodium carboxymethylcellulose	No drug or herbal interactions with sodium carboxymethylcellulose have been reported.		
Sorbitol	Sodium polystyrene sulfonate	Concomitant use has been implicated in cases of colonic necrosis.	Avoid concurrent use.
	Dichlorphenamide	Metabolic acidosis is associated with the use of dichlorphenamide and large volumes of sorbitol.	Avoid concurrent use.
Sodium monofluorophosphate	Calcium	Calcium can form insoluble compounds with fluoride, with consequent reduction in its absorption by 10%–25%.	Avoid concurrent use if possible.

Key: ACEIs = Angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers; CYP = cytochrome P450; DHEA = dehydroepiandrosterone.

Source: References [13](#), [23–25](#), [29–31](#), and [33](#).

Guidelines for brushing teeth can be found in the previous chapter ([Table 31–1](#)) and can be applied to brushing with desensitizing dentifrices.⁹ A single application typically has no effect; for some patients, long-term use (over 4–6 weeks) may be necessary to relieve the symptoms. The desensitizing dentifrice should be used until the sensitivity subsides or for as long as the dentist recommends. If the hypersensitivity is not relieved within 4–6 weeks of using a desensitizing dentifrice, the patient should see a dentist for an in-office method of treatment or an appropriate OHCP for further evaluation.⁸

Product Selection Guidelines

Patients with hypersensitive teeth should be cautioned against using high-abrasion toothpastes such as cosmetic pastes that whiten teeth or remove stains.

Special Populations

Dentifrices containing potassium nitrate 5% are not recommended for children younger than 12 years. Some toothpastes containing potassium nitrate have earned the American Dental Association (ADA) Seal of Acceptance, which means they have been shown to be not only efficacious but also safe. Therefore, no special considerations are necessary in choosing products for pregnant or lactating women or for geriatric patients.

Assessment of Toothache and Tooth Hypersensitivity: A Case-Based Approach

The primary objectives of the assessment are to determine whether the patient has a history of dental problems, whether the patient's oral self-care regimen is adequate, and whether the patient receives regular professional dental care. This information will help determine the patient's level of care and risk for a toothache versus tooth hypersensitivity ([Table 32-1](#)).

Patient Counseling for Tooth Hypersensitivity

Subsequent to a definite diagnosis of tooth hypersensitivity, patients should be counseled on the proper use of desensitizing toothpastes and safe methods of toothbrushing, as outlined in the box "Patient Education for Tooth Hypersensitivity." Use of the desensitizing toothpaste should continue for as long as the dentist recommends, and then switching to a low-abrasion (non-whitening) fluoride dentifrice is appropriate.

Evaluation of Patient Outcomes for Tooth

Hypersensitivity

The patient with tooth hypersensitivity should use a desensitizing dentifrice for at least 4 weeks. If the pain is resolved, the patient should continue treatment as recommended by an OHCP. The patient should be advised to continue the recommended dental hygiene measures (i.e., regular flossing, brushing teeth at least twice daily, and visiting the dentist twice a year). If the pain persists or worsens, or if new symptoms develop after 4–6 weeks, the patient should see the dentist for further evaluation.⁸

Teething Discomfort

Not all babies suffer discomfort during teething. For those who do, nonprescription products can provide symptomatic relief.

Pathophysiology of Teething Discomfort

Teething is the eruption of the deciduous (primary or baby) teeth through the gingival tissues. Usually, this normal physiologic process is essentially uneventful. In some children, however, it can cause pain, sleep disturbances, or irritability.

Clinical Presentation of Teething Discomfort

Mild pain, irritation, reddening, excessive drooling, mouth biting, gum rubbing, low-grade fever, or slight swelling of the gums while teething may precede or accompany sleep disturbances or irritability.¹⁰ Teething is not associated with vomiting, diarrhea, nasal congestion, malaise, fever, or rashes; these signs and symptoms may indicate presence of an ear or gastrointestinal infection. Bluish soft, round swellings (called eruption cysts) sometimes form over emerging incisors and molars. Eruption cysts are not the result of infection and will disappear if left alone. In addition, three bumps, called mamelons, may be present on the biting surfaces (*incisal edges*) of emerging incisors. The mamelons will wear away as the teeth begin to occlude against the opposing

dentition. If the underside of the tongue becomes irritated, a dentist may try to smooth the edges of the mamelons to prevent further irritation. Teeth eruption can begin as early as the age of 3 months, and for each tooth that erupts, the teething period usually extends over an 8-day window.^{10–12}

Patient Education for Tooth Hypersensitivity

The objectives of self-treatment of tooth hypersensitivity are (1) to repair the damaged tooth surface using an appropriate toothpaste and (2) to replace abrasive toothbrushing practices with preferred technique. For most patients, carefully following product instructions, the dentist's recommendations, and the self-care measures listed here will help ensure optimal therapeutic outcomes.

- If adherence to correct brushing techniques with a fluoride toothpaste fails to effect improvement, a desensitizing toothpaste should be used.
- If a desensitizing toothpaste is needed, apply a 1-inch strip of an appropriate dentifrice to a soft-bristle toothbrush and brush at least twice daily.
- Note that relief of the sensitivity may take several days to several weeks. The better the patient is at removing bacterial plaque, the more quickly the sensitivity will resolve.
- Use the dentifrice for as long as the dentist recommends, and then switch to a low-abrasion (non-whitening) fluoride dentifrice.
- Note that some cases of tooth hypersensitivity require long-term treatment or several repeated treatments.
- Do not use desensitizing toothpastes in children younger than 12 years.
- Do not use high-abrasion toothpastes, such as cosmetic pastes that whiten or remove stains.

When to Seek Medical Attention

- see a dentist if the pain worsens during treatment or if new symptoms develop.

Source: [References 2–9](#).

Treatment of Teething Discomfort

Treatment Goals

The goal of self-care for teething discomfort is to relieve gum pain and irritation, thereby reducing the child's distress and sleep disturbances.^{10,12}

General Treatment Approach

Parents and caregivers should be cautioned to exercise restraint in treating a child's teething discomfort. Eruption cysts are a feature of the normal physiologic process and should be left alone to resolve spontaneously. If cut or punctured, the cysts will form scars that may delay the tooth's eruption. Parents should try all nonpharmacologic measures to determine which ones are helpful. If additional treatment is needed, pediatric doses of certain systemic analgesics can be used. Furthermore, the use of teething necklaces should be discouraged, in view of the potential risk of choking and strangulation, versus accessorizing the child with a product that has never been proved to be effective.^{10,11} FDA has additional information and warnings on the agency's website about not using these products.¹⁵

Nonpharmacologic Therapy

If the baby cooperates, massaging the gum around the erupting tooth may provide relief. Babies may be made more comfortable by providing them with a cold teething ring. Teething products made of plastic and filled with fluid should not be subjected to extreme temperatures, as with boiling to sanitize or freezing; such exposure can weaken the plastic, with subsequent leakage of the fluid.^{10,11} The cold temperature causes beneficial local vasoconstriction, in addition to the pressure on the gums that the child feels on biting down on the object. The [HealthyChildren.org](https://www.healthychildren.org) website for parents and caregivers also emphasizes washing the hands first and consideration of light, gentle

massage and providing damp washcloths that have been twisted and frozen. Additional strategies are discussed on the website. If the child is at an age to tolerate food such as dry toast or teething biscuits, such foods may be offered to chew on. Foods high in sucrose should be avoided.^{10,11} The American Dental Association recommends regular dental checkups, which includes a dental visit within 6 months of eruption of the child's first tooth but no later than the child's first birthday.

Pharmacologic Therapy

Pharmacologic management of infant teething discomfort is limited to pediatric doses of certain systemic analgesics. Topical oral anesthetics carry strict warnings from the U.S. Food and Drug Administration (FDA) against their use. Clinically important drug interactions for topical oral anesthetics are listed in [Table 32–3](#).

Topical Oral Anesthetics

Benzocaine is available in concentrations ranging from 5%–20% and is generally not accepted as a safe topical anesthetic for teething pain. In addition, the safety of benzocaine use during pregnancy has not been established.^{11,13} [Table 32–4](#) provides additional information regarding use of benzocaine in pregnancy.¹³ (See the Preface for a detailed explanation of the pregnancy data.)

TABLE 32–4 Selected Nonprescription Medications for Recurrent Aphthous Stomatitis and Herpes Simplex Labialis

Trade Name	Primary Ingredient(s)	Pregnancy Data ^a
Oral Debriding and Wound-Cleansing Agents ^b		
Cankaid Liquid Oral Antiseptic	Carbamide peroxide 10%	Information is not available about the use of carbamide peroxide in pregnancy, but it is unlikely that any significant concentration reaches the fetus. Pregnant patients should consult a dentist along with their primary care provider before considering use of these products. No adequate and well-controlled studies have been conducted in pregnant women.
Gly-Oxide Antiseptic	Carbamide peroxide 10%	

Trade Name	Primary Ingredient(s)	Pregnancy Data^a
Oral Cleanser		
Orajel Antiseptic Rinse for Mouth Sores	Hydrogen peroxide 1.5%	Pregnant patients should consult a dentist along with their primary care provider before considering use of these products. No adequate and well-controlled studies have been conducted in pregnant women.
Colgate Peroxyl Mouth Sore Rinse	Hydrogen peroxide 1.5%	
Topical Oral Anesthetics		
Anbesol Regular Strength Gel/Liquid	Benzocaine 10%	Pregnant patients should consult a dentist along with their primary care provider before considering use of these products. No adequate and well-controlled studies have been conducted in pregnant women.
Zilactin-B Gel	Benzocaine 10%	
Anbesol Maximum Strength Gel	Benzocaine 20%	
Kank-A Liquid	Benzocaine 20%	
Orabase Paste	Benzocaine 20%	
Benzodent	Benzocaine 20%	
Orajel Mouth Sore Gel	Benzocaine 20%; benzalkonium chloride 0.02%; zinc chloride 0.1%	
Campho-	Camphor	Pregnant patients should consult a dentist along with their

Trade Name	Primary Ingredient(s)	Pregnancy Data^a
Phenique Gel/Liquid	10.8%; phenol 4.7%	primary care provider before considering use of these products. No adequate and well-controlled studies have been conducted in pregnant women.
Blistex Lip Medex Ointment	Camphor 1%; menthol 1%; phenol 0.54%; petrolatum 59.14%	
Carmex Lip Balm Ointment	Menthol 0.7%; camphor 1.7%; phenol 0.4%	
Herpicin-L Lip Balm	Dimethicone 1%; meradimate 5%; octinoxate 7.5%; octisalate 5%; oxybenzone 5%	
Topical Oral Protectants^b		
Canker Cover	Menthol 2.5 mg	Pregnant patients should consult a dentist along with their primary care provider before considering use of these products. No adequate and well-controlled studies have been conducted in pregnant women.
Cankermelts	Glycyrrhiza extract (GX) 30 mg (includes 1.4 mg glycyrrhizin) per disc	
Oral Rinses		
Original Listerine Antiseptic	Eucalyptol 0.092%; menthol 0.042%;	Pregnant patients should consult a dentist along with their primary care provider before considering use of these products. No adequate and well-controlled studies have been conducted in pregnant women.

Trade Name	Primary Ingredient(s)	Pregnancy Data ^a
	methyl salicylate 0.060%; thymol 0.064%	
Canker-Rid	Bee propolis	
Topical Treatments^c		
Abreva cream	Docosanol 10%	Pregnant patients should consult a dentist along with their health care provider before considering use of these products. No adequate and well-controlled studies have been conducted in pregnant women.

^a See the Preface for a detailed explanation of the pregnancy data.

^b Use limited to recurrent aphthous stomatitis.

^c Use limited to herpes simplex labialis.

Key: FDA = U.S. Food and Drug Administration; ID = insufficient data to determine pregnancy category. Source: [References 13, 25, 30, and 31](#).

In the highest concentration approved for nonprescription use (20%), benzocaine is too potent for infants and can even cause death from drug overdose.^{11,13} In April 2011, FDA released a MedWatch safety alert that warned health care providers of the reports linking benzocaine use and methemoglobinemias.¹⁴ FDA and the American Academy of Pediatrics no longer recommend the use benzocaine containing products for teething.¹⁵ Patients with known hypersensitivity to common local anesthetics should not use products containing benzocaine. Benzocaine is a known sensitizer (allergen), and its use in these patients can cause a hypersensitivity reaction.

In June 2014, FDA released a Drug Safety Communication regarding the use of topical agents for infant and child teething discomfort.¹⁶ The communication warned that prescription oral viscous lidocaine 2% solution should not be used

to treat infants and children with teething pain. Furthermore, the agency requires the following boxed warning to appear on the product packaging: “Oral viscous lidocaine solution is not approved to treat teething pain, and use in infants and young children can cause serious harm, including death.” In addition, this safety communication recommends against use of nonprescription topical medications for teething pain, which would include benzocaine-containing products. These products are sold under different brand names, such as Anbesol, Hurricaine, Orajel, Baby Orajel, Orabase, and various store brands. FDA supports following the American Academy of Pediatrics’ recommendations to help lessen teething pain. These modalities are discussed in detail earlier in the “Nonpharmacologic Therapy” section.

A warning released by FDA in September 2016 warns of the risk that homeopathic teething tablets and gels can pose to children, including those distributed by CVS, Hyland’s, and possibly other companies, although other manufacturers were not named specifically.¹⁷ FDA recommends that consumers stop using these products immediately and seek medical attention if their child experiences symptoms consistent with belladonna toxicity after using any of these products.¹⁷ Teething should be managed using nonpharmacologic modalities, which are described in detail earlier.

Systemic Analgesics

Pediatric doses of certain systemic nonprescription analgesics (e.g., acetaminophen) may be used to relieve teething discomfort. (See [Chapter 5](#) for discussion of these agents, recommended dosages, clinically important drug interactions, and pregnancy safety data.)

Product Selection Guidelines

Topical teething products labeled for the temporary relief of sore gums due to teething in infants and children are no longer recommended by FDA as safe and effective.^{14–17} Nonpharmacologic measures and certain systemic analgesics, given at the appropriate pediatric doses, should be used for symptom management.

Special Populations

The pediatric population should avoid topical teething products.^{14–17}

Assessment of Teething Discomfort: A Case-Based Approach

In most cases, teething discomfort must be assessed on the basis of the parent's description of the child's symptoms. If the child cooperates, visual inspection of the gums may confirm that the child is teething. Nonetheless, the signs and symptoms of teething must be distinguished from those of an infection.

Patient Counseling for Teething Discomfort

Patient counseling for parents should include both nonpharmacologic and pharmacologic remedies for teething discomfort, as outlined in the box "Patient Education for Teething Discomfort." Parents should be urged to contact a primary care provider when uncharacteristic symptoms of teething discomfort are present.

Evaluation of Patient Outcomes for Teething Discomfort

The parent should be asked to call back after 2 days of treatment. If neither nonpharmacologic measures nor nonprescription medications are relieving the symptoms, the parent should be advised to take the baby to a pediatrician, pediatric dentist, or other primary care provider. Furthermore, if symptoms uncharacteristic of teething discomfort have developed, the baby should be evaluated by an appropriate primary care provider.

Patient Education for Teething Discomfort

The objective of parent or caregiver self-treatment for teething discomfort is to relieve gum pain and irritation, thereby reducing the affected child's

distress and sleep disturbances. For most patients, the parent's or caregiver's careful following of product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

Nondrug Measures

- If possible, massage the gum around the erupting tooth to provide relief.
- Give the baby a cold teething ring or cold wet cloth or an appropriate food (e.g., dry toast or teething cookies) to chew on.
- The American Dental Association recommends regular dental checkups, which includes a dental visit within 6 months of eruption of the child's first tooth but no later than the child's first birthday.

Nonprescription Medications

Topical Analgesics

- Do not use teething preparations containing benzocaine in infants and young children.
- Do not use prescription viscous lidocaine 2% solution in infants and young children.

Systemic Analgesics

- If desired, use pediatric formulations of certain oral nonprescription analgesics such as acetaminophen to relieve teething discomfort.
- Read the label carefully, and do not exceed recommended doses or frequency of use.

When to Seek Medical Attention

- If the baby is vomiting or has diarrhea, fever, nasal congestion, malaise, pain, or other symptoms not typical of teething discomfort, take the baby to a pediatrician or other primary care provider.

Source: [References 10–17](#).

Recurrent Aphthous Stomatitis

Recurrent aphthous stomatitis (RAS), in which the lesions are also known as canker sores or aphthous ulcers, and can affect up to 25% of the general population.¹⁸ Eighty percent of patients with RAS are considered to have a mild form of the disease.¹⁸ The lesions affect only nonkeratinized mucosa (e.g., labial, buccal) and will spontaneously heal in 10–14 days.^{18,19}

Pathophysiology of Recurrent Aphthous Stomatitis

The cause of RAS is unknown in most patients. Precipitating factors such as local, systemic, immunologic, genetic, allergic, and nutritional factors have been proposed. Local trauma (e.g., smoking, chemical irritation, biting the inside of cheeks or lips, injury caused by toothbrushing or braces) has been implicated as a leading cause of lesions.^{18,19} Streptococci and varicella-zoster virus have been implicated as infectious agents.^{18,19} Systemic conditions associated with RAS include Behçet disease, systemic lupus erythematosus, neutrophil dysfunction, inflammatory bowel disease, and human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS). Nutritional conditions associated with RAS include gluten-sensitive enteropathy and deficiencies of iron, B vitamins (B₁, B₂, B₆, B₁₂), and folic acid.

Clinical Presentation of Recurrent Aphthous Stomatitis

RAS manifests as an epithelial ulceration on nonkeratinized mucosal surfaces of movable mouth parts, such as the tongue, floor of the mouth, soft palate, or inside lining of the lips and cheeks. Rarely, ulcerations affect keratinized tissue such as the gingiva or the external lips (vermilion). Individual ulcers are usually (1) round or oval, (2) flat or *crateriform* (having a depressed, crater-like center), and (3) gray to grayish yellow, with an erythematous halo of inflamed tissue surrounding the ulcer (see [Color Plates](#), photograph 13).

RAS occurs in three clinical forms: minor, major, and herpetiform. The RAS form can be distinguished primarily by the number of lesions, the size of the ulcer, and the number of days that the lesion persists. [Table 32–5](#) compares the features of the three forms of RAS and cold sores.^{18–21} Some patients may experience a pricking or burning sensation (prodrome) approximately 2–48 hours before the lesion actually appears.²⁰ The lesions can be very painful, with the pain increasing with eating and drinking, and normal functions including eating, drinking, swallowing, talking, and routine oral hygiene may be severely limited. Usually, fever or lymphadenopathy does not accompany RAS; however, such signs and symptoms may arise if a secondary bacterial infection is present.

TABLE 32–5 Differentiation of Recurrent Aphthous Stomatitis (RAS) and Herpes Simplex Labialis (HSL)

	RAS (“canker sores”)		HSL (“cold sores”)	
Feature	Minor	Major	Herpetiform	Recurrent
Clinical manifestation	Oval, flat ulcer; erythematous tissue around ulcer	Oval, ragged, gray/yellow ulcers; crateriform	Small, oval ulcers in crops, similar to minor RAS	Red, fluid-filled vesicles; lesions may coalesce; crusted when mature
Location	All areas except gingiva, hard palate, vermillion border (at junction of oral mucosa and external skin)	Any intraoral area, but predilection for lips, soft palate, and throat	Any intraoral area	Junction of oral mucosa and skin of lip and nose
Incidence	13%–26%	1.5%–3%	0.5%–1%	20%–30%
Incidence among RAS sufferers	80%	10%	5%–10%	n/a
Number of lesions	1–5	Several (1–10)	10–100 (in crops)	Several
Size of lesion	<0.5 cm	>0.5 cm	<0.5 cm	1–3 mm
Duration	10–14 days	≥6 weeks	7–10 days	10–14 days

	RAS (“canker sores”)		HSL (“cold sores”)	
Feature	Minor	Major	Herpetiform	Recurrent
Pain	None-moderate	None-moderate	Moderate-severe	None-moderate
Scarring	None	Common	None	Rare
Comments	Immunologic defect	Immunologic defect	Immunologic defect	Induced by HSV-1

Key: HSV-1 = Herpes simplex virus type 1; n/a = not applicable.

Source: [References 18, 20, 22, 32, 38](#), and [46](#).

Algorithm: Recurrent Aphthous Stomatitis

FIGURE 32–2 Self-care for recurrent aphthous stomatitis (RAS). Key: D/C = Discontinue; HSL = herpes simplex labialis; OTC = over-the-counter. (Source: [References 13 and 18–30](#).)

Treatment of Recurrent Aphthous Stomatitis

RAS cannot be cured; however, nonprescription medications can provide symptomatic relief.

Treatment Goals

The primary objective of self-treatment for RAS is to relieve pain and irritation so that the lesions can heal and the patient can eat, drink, and perform routine oral hygiene. The secondary objective is to prevent complications, such as secondary infection, and to deter recurrence.²²

General Treatment Approach

If possible, the lesions should be inspected to determine whether their

appearance and location are characteristic of RAS. If possible, factors that may have led to development of the ulcer should be identified, and precipitating or contributing factors should be removed. For example, if local trauma is suspected, perhaps a softer toothbrush and gentler brushing technique could be suggested. It also is helpful to determine whether the patient has a history of RAS. If the treatments used are appropriate and previously have been successful for the patient, they should be continued. [Figure 32–2](#) outlines the self-treatment for RAS and lists exclusions for self-care.^{13,18,19,22,23}

Nonpharmacologic Therapy

If a nutritional deficiency (e.g., iron, folate, vitamins) is diagnosed as a contributing factor, the patient should increase consumption of foods high in the deficient nutrients or take appropriate nutritional supplements. For patients in whom a food allergy is thought to be a contributing factor, elimination of the offending agent from the diet may help to control or resolve RAS. The box “Patient Education for Recurrent Aphthous Stomatitis” lists additional nonpharmacologic measures.

Pharmacologic Therapy

Several types of nonprescription medications (oral debriding and wound-cleansing agents, topical oral anesthetics, topical oral protectants, oral rinses, certain systemic analgesics) provide symptomatic relief of RAS, but they do not prevent its recurrence. [Table 32–4](#) lists a variety of the commercially available products for relief of orofacial pain and discomfort and their pregnancy category risk rating, if known.

Clinically important drug interactions with these agents—oral debriding and wound-cleansing agents, topical oral anesthetics, topical oral protectants, and oral rinses—are discussed in [Table 32–3](#).

Oral Debriding and Wound-Cleansing Agents

It is reasonable to begin treatment with topical medication and advance to systemic medication as necessary, with a goal of decreasing recurrence rate and severity of the outbreaks of RAS. Oral debriding agents and wound cleansers may be used (1) to aid in the removal of debris, phlegm, mucus, or other secretions associated with a sore mouth; (2) to cleanse minor wounds or

areas of minor gum inflammation; and (3) to cleanse recurrent aphthous ulcers. Products that release nascent oxygen can be used as debriding and cleansing agents to provide temporary relief of RAS discomfort.²⁵ Hydrogen peroxide and carbamide peroxide release oxygen immediately on contact with tissue enzymes (catalase and peroxidase), but tissue and bacterial exposure to the oxygen is very brief.^{23,24}

For direct application, a few drops of carbamide peroxide (10%–15%) or hydrogen peroxide (1.5%) are applied to the affected area and allowed to remain in place for 1 minute before expectorating. This can be done up to 4 times a day. As a rinse, carbamide peroxide drops are placed on the tongue, mixed with saliva, and swished in the mouth for 1 minute. An aqueous solution of hydrogen peroxide 3% should be mixed with an equal amount of water before rinsing the mouth. Prolonged rinsing with oxidizing products can lead to soft tissue irritation, transient tooth sensitivity from decalcification of enamel, cellular changes, and overgrowth of undesirable organisms that could possibly result in development of a black hairy tongue.²³

Self-medication with any of these products should not be continued for longer than 7 days, and patients should contact an OHCP if symptoms (i.e., irritation or inflammation of the mouth or throat) worsen or persist beyond that time. If at any time a rash develops during the self-treatment regimen, the patient should discontinue use of the product and contact an OHCP. These products should be used after meals (3–4 times a day), and the patient should avoid eating or drinking for at least 30 minutes after application. The patient is directed to swish the liquid around the mouth for 10–15 minutes (or as long as tolerated, but no longer than 15 minutes). It is important not to swallow these medications.

Topical Oral Anesthetics

Topical oral anesthetic/analgesic products, including benzocaine 5%–20%, benzyl alcohol 0.05%–0.1%, dyclonine 0.05%–0.1%, and hexylresorcinol 0.05%–0.1%, generally are recognized as effective for temporary relief of pain associated with RAS.^{25,26} These are the active ingredients in certain products including Anbesol, Blistex, Orajel, and Benylin. It is important to avoid the concurrent use of potentially inflammatory products containing substantial amounts of menthol, phenol, or camphor. These agents may cause tissue irritation and damage or systemic toxicity. To reduce the incidence of RAS,

patients should also avoid the use of dentifrices containing sodium lauryl sulfate.^{18–21}

Topical Oral Protectants

Oral mucosal protectants such as denture adhesives are pharmacologically inert substances that coat and protect the ulcerated area. Coating the ulcer with a topical oral protectant can be effective in protecting ulcerations, decreasing friction, and giving temporary symptomatic relief. These products create a barrier by using a paste, an adhering film, or a dissolvable patch to cover the lesion. Some products are available in combination with an oral anesthetic. Products available as a patch or dissolving disc must be placed against the sore for 10–20 seconds. Once the disc adheres to the lesion, the barrier is formed and the disc will stay in place until dissolved, approximately 8–12 hours.²⁷ A study from Istanbul found that a mucoadhesive biopatch containing citrus essential oil resulted in satisfying pain alleviation and restoration of oral functions, with a significant improvement in oral health-related quality of life.²⁸

Patient Education for Recurrent Aphthous Stomatitis

The primary objective of self-treatment of recurrent aphthous stomatitis is to relieve pain and irritation so that the lesions can heal and the patient can eat, drink, and perform routine oral hygiene. The secondary objective is to prevent complications, such as secondary infection. For most patients, carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

Nondrug Measures

- If a deficiency of iron, folate, or vitamin B₁₂ is diagnosed as a contributing factor, increase consumption of foods high in the deficient nutrient, or take appropriate nutritional supplements.
- Avoid spicy or acidic foods until the lesions heal.
- Avoid sharp-textured foods that may cause increased trauma to the lesion.
- If desired, apply ice directly to the lesions in 10-minute increments

but for no longer than 20 minutes in a given hour.

- Do not use heat. If an infection is present, heat may spread the infection.

Nonprescription Medications

- If longer-lasting relief is desired, nonprescription medications such as oral debriding and cleansing agents, topical oral anesthetics, topical oral protectants, oral rinses, and certain systemic analgesics can be used.

Oral Debriding and Wound-Cleansing Agents

- Use a product containing one of the following ingredients: carbamide peroxide 10%–15% or hydrogen peroxide 1.5%. Apply after meals up to 4 times daily.
- Do not use these medications longer than 7 days. Chronic use can cause tissue irritation, decalcification of enamel, and black hairy tongue.
- Do not swallow these medications.

Topical Oral Anesthetics

- Use products containing one of the following medications: benzocaine 5%–20%, benzyl alcohol 0.05%–0.1%, dyclonine 0.05%–0.1%, or hexylresorcinol 0.05%–0.1%.
- Do not use benzocaine if you have a history of hypersensitivity to other benzocaine-containing products.

Topical Oral Protectants

- Use topical oral protectants or denture adhesives to coat and protect the lesions. These agents also will provide temporary relief of discomfort.
- Apply these products as needed.

Oral Rinses

- Rinse the mouth with Original Listerine Antiseptic to hasten healing of the lesions.
- Rinse the mouth with a saline solution to soothe discomfort or to prepare the lesion for application of a topical medication. For saline solution, add 1–3 teaspoons of salt to 4–8 ounces of warm tap water.

Systemic Analgesics

- Certain oral analgesics (e.g., aspirin or other NSAID, acetaminophen) can be used for additional relief of mouth discomfort.
- Do not hold an aspirin tablet in the mouth or place it on oral lesions. The acetylsalicylic acid can cause a chemical burn and tissue damage.

When to Seek Medical Attention

- See a primary care provider for any of the following outcomes:
 - Symptoms do not abate after 7 days of treatment with oral debriding or wound-cleansing agents.
 - The lesions do not heal in 14 days.
 - Symptoms worsen during self-treatment.
 - Manifestations of systemic infection, such as fever, rash, or swelling, develop.

Key: NSAID = Nonsteroidal anti-inflammatory drug.

Source: [References 13](#) and [18–30](#).

Oral Rinses

Rinsing the mouth with an antiseptic rinse will hasten the healing of the lesions. Saline rinses (1–3 teaspoons of salt in 4–8 ounces of warm tap water) may soothe ulcers and can be used before topical application of a medication. This can be used up to 4 times a day. Similarly, a paste of baking soda applied to the lesions for a few minutes may soothe irritation.

Systemic Analgesics

Certain systemic nonprescription analgesics (e.g., aspirin, nonsteroidal anti-inflammatory drugs, acetaminophen) give additional relief of mouth discomfort. (See [Chapter 5](#) for discussion of these agents, recommended dosages, clinically important drug interactions, and pregnancy safety data.) Aspirin tablets should not be retained in the mouth before swallowing, nor placed in the area of the oral lesions. The acetylsalicylic acid can cause a chemical burn with subsequent tissue damage (see [Color Plates](#), photograph 14).

Product Selection Guidelines

Patients with known hypersensitivity to common local anesthetics should not use any product containing a local anesthetic. Benzocaine is a known sensitizer (allergen), and its use in these patients can cause a hypersensitivity reaction. Patients with known sensitivity to aspirin also should avoid salicylic acid. Various dosage forms are available (e.g., liquid, gel, rinse, dissolvable patch); drug delivery is a major concern, however, because topical applications can be easily washed away by saliva. Gels are the preferred drug delivery application because they are easy to apply and are not as easily washed away.^{18–22,27–29} A topical anesthetic will provide short-term relief of the pain and discomfort associated with RAS, and the oral debriding agents will help to keep the ulcer clean. Using both types of agents should help alleviate immediate discomfort and heal the ulcer quickly.

Special Populations

The safety of these agents (oral debriding and wound-cleansing agents, topical oral anesthetics, topical oral protectants, and oral rinses) with use during pregnancy is mostly unknown. [Table 32–4](#) provides additional information regarding use of these agents. (See the Preface for detailed explanation of the pregnancy data.) No special considerations are necessary in choosing products for older adults. It is unknown how these products affect lactating women. These products should not be used or are not approved for use in pediatric patients.^{13,23,24,30–32}

Assessment of Recurrent Aphthous Stomatitis: A Case-Based Approach

Controlling the pain and preventing infection are the primary concerns when RAS is suspected. If possible, factors that may have precipitated or contributed to the development of the ulcer should be identified and then removed. The patient should be asked about previous self-treatments and their effectiveness. If the treatments used are appropriate and have been successful for the patient, they should be continued. Case 32–1 provides an example of the assessment of a patient with RAS.

Patient Counseling for Recurrent Aphthous Stomatitis

All nonpharmacologic and pharmacologic measures for treating RAS, as outlined in the box “Patient Education for Recurrent Aphthous Stomatitis,” should be explained to the patient. The patient should also be cautioned about using ineffective or harmful therapies. Possible adverse effects, drug interactions, contraindications, and precautions should then be explained for all nonprescription agents. In addition, patients must be alerted to the conditions that warrant dental or medical evaluation.

Case 32–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient’s symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity,	Patient noticed a burning/prickling sensation about a day ago. On looking in her mouth, she noticed a

Relevant Evaluation Criteria	Scenario/Model Outcome
associated symptoms)	grayish oval-shaped lesion with a bumpy-appearing surface.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Patient started a smoking cessation program at your pharmacy 2 weeks ago and has been smoke free for 1 week.
c. Description of the patient's efforts to relieve the symptoms	Patient has not tried anything yet.
d. Patient's identity	Rebecca Sithgib
e. Patient's age, gender, height, and weight	32 years, female, 5 ft 9 in., 155 lb
f. Patient's occupation	High school German teacher
g. Patient's dietary habits	Excellent eater, although she admits to having a "sweet tooth."
h. Patient's sleep habits	6–8 hours nightly
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Multivitamin once daily for 2 years; NuvaRing for 2 months
j. Allergies	NKDA
k. History of other adverse reactions to medications	None
l. Other (describe) _____	n/a
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Given the location and appearance of the lesion, it is highly likely that the patient has recurrent aphthous stomatitis (see Table 32–5). She is at high risk for developing this condition because she just quit smoking and also recently started using NuvaRing, associated with fluctuation in hormone levels.

Relevant Evaluation Criteria	Scenario/Model Outcome
3. Identify exclusions for self-treatment.	None (see Figure 32-2)
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer Ms. Sithgib to her OHCP or other primary care provider. (2) Recommend an OTC product to relieve her discomfort. (3) Recommend nondrug measures. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Use of an oral debriding/cleansing agent (e.g., Peroxyl) and a topical anesthetic (e.g. Anbesol) would be an appropriate initial option. (See Table 32-4 for a complete list of appropriate options.)
6. Describe the recommended therapeutic approach to the patient or caregiver.	"A topical anesthetic will provide short-term relief of the pain and discomfort. An oral debriding/cleansing agent will help to keep the ulcer clean to aid in healing."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Using both of these agents should help to ease your discomfort as well as heal the ulcer quickly. If you are not experiencing pain or discomfort, the topical anesthetic does not need to be used."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	"The debriding/cleansing mouth rinse can be used up to 4 times a day (after meals)." See the box "Patient Education for Recurrent Aphthous Stomatitis."
Solicit follow-up questions from the patient or caregiver.	"Should I maintain my normal oral hygiene routine?"

Relevant Evaluation Criteria	Scenario/Model Outcome
Answer the patient's or caregiver's questions.	"Yes. Continue to brush and floss twice a day, and use a toothpaste that contains fluoride."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Ask Ms. Sithgib to call to update you on her response to your recommendations, or you could call her in a week to evaluate her response.

Key: n/a = Not applicable; NKDA = no known drug allergy; OHCP = oral health care provider; OTC = over-the-counter.

Evaluation of Patient Outcomes for Recurrent Aphthous Stomatitis

Minor RAS lesions typically are self-limiting and resolve within 14 days. Oral debriding and wound-cleansing agents are labeled for use for up to 7 days. If the symptoms have abated, the patient should discontinue treatment but continue other dental hygienic measures (e.g., regular flossing and twice-daily toothbrushing). Symptoms that persist or worsen during treatment necessitate medical evaluation.

Minor Oral Mucosal Injury or Irritation

Pathophysiology of Minor Oral Mucosal Injury or Irritation

Minor wounds or inflammation resulting from minor dental procedures; accidental injury (e.g., biting of the tongue, cheek or abrasion from sharp, crisp foods); or other irritations of the mouth, gums, or palate may be treated with

various nonprescription medications.

Algorithm: Minor Oral Mucosal Injury or Irritation

FIGURE 32–3 Self-care for minor oral mucosal injury or irritation. Key: D/C = Discontinue. (Source: [References 23–26, 29, 30, 33, and 35.](#))

Treatment of Minor Oral Mucosal Injury or Irritation

Treatment of mouth injury (traumatic laceration or ulcer) and irritation is similar to that for RAS. Mouth injury and irritation differ from RAS with regard to etiology and certain treatment considerations.

Treatment Goals

The goals of treating minor mucosal injury and irritation are (1) to control discomfort and pain, (2) to aid healing with the appropriate use of nonpharmacologic and pharmacologic measures, and (3) to prevent secondary bacterial infection.

General Treatment Approach

Treatment should focus first on relieving discomfort, readily accomplished with application of ice. Local anesthetics, certain oral analgesics, and saline rinses also are safe and effective.^{18,19,22} Once the discomfort has resolved, the focus should be on healing the affected area. Homemade sodium bicarbonate rinses and oral debriding and wound-cleansing agents can help achieve this objective. Finally, concomitant use of oral protectants can relieve discomfort and aid healing by protecting the area from further irritation. [Figure 32–3](#) outlines this approach and lists exclusions for self-care.^{23–25,29,33}

Nonpharmacologic Therapy

When tissues of the lips, tongue, cheeks, or palate are bruised, topical application of ice wrapped in a cloth or other barrier may reduce the swelling. Ice should be applied in 10-minute increments but not longer than 20 minutes in a given hour. Longer application times may cause local tissue damage.

Sodium bicarbonate solutions (1/2–1 teaspoon of household baking soda in 4 ounces of water) can act as an oral debriding agent and wound cleanser.^{34,35} The solution is swished in the mouth over the affected area for at least 1 minute and then expectorated. Sodium bicarbonate's mucolytic action is related to its alkalinity. Saline rinses (1–3 teaspoons of salt in 4–8 ounces of warm tap water) can cleanse and soothe the affected area.^{26,34,36} Both sodium bicarbonate and saline rinses can be used up to 4 times a day.

Pharmacologic Therapy

As with RAS, topical analgesics/anesthetics, oral protectants, and oral debriding and wound-cleansing agents constitute the mainstay of pharmacologic therapy. The “Pharmacologic Therapy” section under “Treatment of Recurrent Aphthous Stomatitis” discusses these agents in further detail. In addition to these various agents, astringents may be used. Astringents cause tissues to contract or arrest secretions by causing proteins to coagulate on the cell surface.³⁷ Dentists may suggest use of oxidizing mouth rinses or topically applied steroids (which are available only by prescription) as an adjunctive treatment for specific conditions or as a postoperative aid in cleaning the affected area, relieving discomfort, and assisting the healing process.

Assessment of Minor Oral Mucosal Injury or Irritation: A Case-Based Approach

The cause and nature of the injury or irritation are the primary considerations in patient assessment. If the disorder is self-treatable, the OHCP should ascertain whether the injury or irritation has occurred previously, how it was treated, and whether the patient has known contraindications to the nonprescription medications used to treat the disorder.

Patient Counseling for Minor Oral Mucosal Injury or Irritation

Once the problem is determined to be a minor irritation or injury of the mouth, the patient should be counseled on (1) the steps in the treatment regimen; (2) the purpose of each agent; and (3) the length of time the products can be used safely. Signs and symptoms that indicate infection should be explained. See the box “Patient Education for Minor Oral Mucosal Injury or Irritation.”

Patient Education for Minor Oral Mucosal Injury or Irritation

The objectives of self-treatment of minor oral mucosal injury or irritation are (1) to control discomfort and pain, (2) to aid healing with the appropriate use of drug and nondrug measures, and (3) to prevent secondary bacterial infection. For most patients, carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

Nondrug Measures

- Rinse with a sodium bicarbonate solution to remove injured tissue and cleanse the affected area. Add 1/2–1 teaspoon of sodium bicarbonate to 4 ounces of water. Swish the solution in the mouth over the affected area for at least 1 minute, and then spit out the solution. This can be done up to 4 times a day.
- Use saline rinses to cleanse and soothe the affected area. Add 1–3 teaspoons of salt to 4–8 ounces of warm tap water. This can be done up to 4 times a day.
- For bruised lips or cheeks, apply ice in 10-minute increments to reduce swelling. Do not apply ice for longer than 20 minutes in a given hour.

Nonprescription Medications

- If longer-lasting relief is desired, use the following types of nonprescription medications: oral debriding and wound-cleansing agents, astringents, topical oral anesthetics, topical oral protectants, and certain systemic analgesics.

Debriding and Cleansing Agents

- Use a product containing carbamide peroxide 10%–15% or hydrogen peroxide 1.5%.
- Do not use these medications for longer than 7 days. Chronic use can cause tissue irritation, decalcification of enamel, and black hairy tongue.
- Do not swallow these medications.
- These products should be used after meals (3–4 times a day), and the patient should avoid eating or drinking for at least 30 minutes after application. Swish the liquid around the mouth for 10–15 minutes (or as long as the patient can tolerate, but no longer than 15 minutes).

Topical Oral Anesthetics

- Use a product containing one of the following medications: benzocaine 5%–20%, benzyl alcohol 0.05%–0.1%, dyclonine 0.05%–0.1%, or hexylresorcinol 0.05%–0.1%.
- Do not use benzocaine if you have a history of hypersensitivity to other benzocaine-containing products.
- Avoid potentially inflammatory products containing substantial amounts of menthol, phenol, or camphor. These agents may cause tissue irritation and damage or systemic toxicity.
- These products should be used after meals (3–4 times a day), and the patient should avoid eating or drinking for at least 30 minutes after application.

Topical Oral Protectants

- Use topical oral protectants or denture adhesives to coat and protect the lesions.
- These products should be used after meals (3–4 times a day), and

the patient should avoid eating or drinking for at least 30 minutes after application.

Systemic Analgesics

- If desired, take an oral analgesic (e.g., aspirin or other NSAID, acetaminophen) for additional relief of mouth discomfort.
- Do not hold aspirin in the mouth or place it on oral lesions. The acetylsalicylic acid can cause a chemical burn and tissue damage.

When to Seek Medical Attention

- See a primary care provider if any of the following occur:
 - Symptoms persist after 7 days of treatment.
 - Symptoms worsen during self-treatment.
 - Manifestations of systemic infection such as fever, redness, or swelling develop.

Key: NSAID = Nonsteroidal anti-inflammatory drug.

Source: [References 23–25, 29, 30, 33, and 35](#).

Evaluation of Patient Outcomes for Minor Oral Mucosal Injury or Irritation

Minor injury or irritation should resolve within 7 days of treatment and within 10 days of the initial insult or injury.³⁷ If the symptoms resolve, no further treatment is necessary. If symptoms persist or worsen, or swelling, rash, or fever develops, the patient should be evaluated by a primary care provider.

Herpes Simplex Labialis

Herpes simplex labialis (HSL), manifesting as cold sores or fever blisters, is a disorder caused by a virus of the family Herpesviridae. Herpes simplex virus

type 1 (HSV-1) is primarily associated with oral and labial lesions, whereas herpes simplex virus 2 (HSV-2) usually produces genital sores. However, predilection of a specific HSV infection for an anatomic site is changing, in part because of variability in sexual practices.^{38,39} Any of the human herpesviruses (e.g., cytomegalovirus, Epstein–Barr virus), not just HSV-1 and HSV-2, can cause oral lesions. Anyone who comes in contact with the herpesvirus can potentially become infected. After the primary infection, HSV infection can be latent and reactivate at a later date as the more commonly known herpes labialis, or cold sores.^{38,39}

Pathophysiology of Herpes Simplex Labialis

HSV infection is contagious and believed to be transmitted by direct contact. Fluid from herpes vesicles contains live virus, which can be transmitted from patient to patient. Because the virus remains viable on surfaces for several hours, contaminated objects also may be a source of infection. Transmission commonly occurs through kissing or sharing utensils or drinking vessels.^{34,38} HSV enters the host through a break in the skin or intact mucous membranes. Once the virus has infected a host, it remains in a latent state in the trigeminal ganglia. The virus can be reactivated on exposure to a triggering stimulus, such as ultraviolet radiation, stress, fatigue, cold, or windburn. Other possible triggers include fever, injury, menstruation, dental work, infectious diseases, and factors that suppress the immune system (e.g., chemotherapy, radiation therapy).^{38,39} Although the virus can go through periods of dormancy and reactivation, the person is infected for life. On reactivation, the lesions often arise repeatedly in the same location.

Clinical Presentation of Herpes Simplex Labialis

HSL is so named because it commonly affects the lip or areas bordering the lips; the usual site is at the junction of mucous membrane and skin of the lips or nose. HSL lesions also may occur intraorally (primarily involving keratinized mucosa such as the hard palate). The lesions are recurrent, painful, and cosmetically objectionable. Onset of HSL often is preceded by a prodrome in which the patient notices burning, *pruritus* (itching), tingling, or numbness in

the area of the forthcoming lesion. Patients experience the prodromal stage approximately 2–48 hours before the lesion actually appears.²⁰ Other signs and symptoms may include pain, fever, localized bleeding, swollen lymph nodes, and malaise.

The initial lesion in an episode of HSL is a collection of small red papules of fluid-containing vesicles 1–3 mm in diameter. Often, many lesions coalesce to form a larger area of involvement. An erythematous, inflamed border around the fluid-filled vesicles may be present. In mature lesions, a crust often forms over the top of many coalesced, burst vesicles; its base is erythematous (see [Color Plates](#), photograph 15). Presence of pustules or pus under the crust of a herpesvirus lesion may indicate a secondary bacterial infection; prompt evaluation and treatment with a targeted antibiotic, if indicated, are appropriate. [Table 32–5](#) further describes the clinical presentation of HSL and compares its features with those of RAS.

A related disease, acute (primary) herpetic gingivostomatitis, is seen mainly in children but can occur in adults, especially those who are immunocompromised. Although the oral lesions of this disease can develop anywhere on the oral mucosal surface, they commonly occur on the lips, areas bordering the lips, or the gums. Herpetic gingivostomatitis is distinguished from RAS gingivostomatitis by infected gums, which are very red and covered by a pseudomembrane or studded with ulcerations. Other symptoms of herpetic gingivostomatitis may include submandibular lymphadenitis, swallowing difficulties, and halitosis. Referral to an appropriate health care provider is warranted if this disorder is suspected.

On the basis of clinical appearance, HSL and RAS should be easy to distinguish from oral candidiasis, which develops as part of yeast infections. In the mouth, candidiasis is often referred to as thrush and is characterized by white plaques with a milk curd appearance. These plaques, seen on the oral mucosa, usually can be detached easily, revealing erythematous, bleeding, sore areas beneath (see [Color Plates](#), photograph 12). Patients with signs of oral candidiasis should be referred for medical evaluation and should not self-treat.

Treatment of Herpes Simplex Labialis

Although HSL and RAS differ in etiology, overall treatment for these disorders

is similar. The patient should be instructed to avoid circumstances that induce more lesions (e.g., stress), to keep the lesions free of counterirritants, and to keep existing lesions as clean as possible, thereby avoiding secondary infections. [Table 32–4](#) lists common classes of nonprescription medications used to treat RAS and HSL. (Note: Of the products listed in [Table 32–4](#), oral debriding and wound-cleansing agents and oral mucosal protectants are *not* used to treat HSL.)

Treatment Goals

The objectives of self-treatment for HSL (cold sores) are (1) to relieve pain and irritation while the sores are healing, (2) to prevent secondary infection, and (3) to curtail spread of the lesions.

General Treatment Approach

The lesions should be inspected to determine whether their appearance and location are characteristic of HSL. If possible, agents or practices that may have led to development of lesions should be identified, so that precipitating or contributing factors can be removed. For example, if trauma is suspected, perhaps a softer toothbrush and gentler brushing technique could be suggested. It also is helpful to ascertain whether the patient has a history of HSL. The medical history should be reviewed to determine whether an underlying pathologic process predisposes the patient to recurrent HSL or could complicate treatment. The interviewing health care provider should inquire about previous self-treatments and their effectiveness. If the treatments used are appropriate and have been successful for the patient, they should be implemented and continued. Treatment should focus on cleansing the affected area, protecting the lesions from infection, and relieving the discomfort of burning, itching, and pain. [Figure 32–4](#) outlines self-treatment for HSL and lists exclusions for self-care.^{28–35,38,39}

Nonpharmacologic Therapy

Lesions should be kept clean by gently washing with mild soap solutions. Handwashing is important in preventing lesion contamination and minimizing autoinoculation of herpesvirus. The involved skin should be kept moist to prevent drying and *fissuring* (cracking). Cracking may render lesions more

susceptible to secondary bacterial infection, may delay healing, and usually increases discomfort. Factors that delay healing (e.g., stress, local trauma, excessive wind or sun exposure, fatigue) should be avoided. Patients who identify sun exposure as a precipitating event should be advised to routinely use an appropriate sunscreen product on the lips and face. (See [Chapter 39](#) for more detail about sunscreens and sun protection factor [SPF] requirements.)

Pharmacologic Therapy

Topical skin protectants help to protect the lesions from infection, relieve dryness, and keep the involved tissue soft, but they do not reduce the duration of symptoms. These products should be used after meals (3–4 times a day), and the patient should avoid eating or drinking for at least 30 minutes after application.²²

Externally applied analgesics or anesthetics, in bland, emollient vehicles, also relieve the discomfort of burning, itching, and pain, but they do not reduce the duration of symptoms. Ingredients that are generally used include benzocaine 5%–20%, dibucaine 0.25%–1%, dyclonine hydrochloride 0.5%–1%, benzyl alcohol 10%–33%, camphor, and menthol. Menthol in concentrations greater than 1% and camphor in concentrations greater than 3% can stimulate cutaneous sensory receptors and produce a counterirritant effect; such preparations are therefore contraindicated.³²

Docosanol 10% (Abreva Cream) is the only FDA-approved nonprescription product proven to reduce the duration and severity of symptoms. The agent inhibits direct fusion between the herpesvirus and the human cell plasma membrane, thereby preventing viral replication.^{31,37} Docosanol should be applied at the first sign of an outbreak (prodromal stage), 5 times a day, until the lesion is healed, but for no more than 10 days. Treatment with docosanol reduces the median healing time to healing by approximately 1 day (18 hours) compared with placebo.⁴⁰ Docosanol-treated patients also note a significant reduction in the duration of symptoms, including pain and/or burning, itching, or tingling, compared with placebo (20% reduction in the median time to complete cessation of these symptoms).³⁸ The safety of docosanol with use during pregnancy is unknown. [Table 32–4](#) provides additional information regarding use of docosanol. (See the Preface for detailed explanation of the pregnancy data.) Clinically important drug interactions with docosanol are discussed in [Table 32–3](#).

Abreva Cream, which contains docosanol 10%, should not be mistaken for Abreva Conceal, which is a nonmedicated patch.³¹

If evidence of secondary bacterial infection is seen (e.g., failure of crusting to occur, persistence of an erythematous border), topical application of a thin layer of triple-antibiotic ointment 3–4 times daily may be recommended as a nonprescription option.^{41,42} (See [Chapter 41](#) for more information about these agents.) Follow-up evaluation by a physician may be indicated if this occurs. Mupirocin ointment or calcium hydroxide/chlorhexidine paste may also be effective, but these are prescription products. Certain systemic nonprescription analgesics may provide additional pain relief.

HSL is not considered a steroid-responsive dermatosis, so the use of topical steroids is contraindicated. Products that are highly astringent also should be avoided. Zinc sulfate should be avoided as well, because oral mucosal absorption and toxicity could occur with frequent application of these agents to the lip and other tissue adjoining the oral cavity.³⁰

Complementary Therapies

The essential oil of *Melaleuca alternifolia*, or tea tree oil, has been shown to have activity against HSV in vitro.⁴³ Although some data are conflicting, lysine may have a preventive effect and may decrease the frequency of outbreaks when taken daily.^{39,44} Extract of the leaves of *Melissa officinalis*, or lemon balm, also has been used in patients with HSL. Studies comparing lemon balm with placebo have shown a reduction in symptoms, shortened healing time, prevention of infection spread, and patient preference for lemon balm.⁴⁵

Algorithm: Herpes Simplex Labialis

FIGURE 32–4 Self-care for herpes simplex labialis (HSL). Key: D/C = Discontinue; OTC = over-the-counter; RAS = recurrent aphthous stomatitis. (Source: [References 26, 29–34, and 36–41.](#))

Assessment of Herpes Simplex Labialis: A

Case-Based Approach

Although many of the same nonprescription medications are indicated for RAS and HSL, the disorders still need to be differentiated. Because herpes simplex lesions are contagious, additional measures are necessary to prevent transmission of the virus. The medical history will help determine the presence of an underlying pathologic process that predisposes the patient to recurrent HSL or could complicate treatment. Case 32–2 provides an example of the assessment of a patient with herpes simplex labialis.

Patient Counseling for Herpes Simplex Labialis

Patient counseling should emphasize that HSL lesions are contagious and should include appropriate measures to prevent transmission of the virus, as outlined in the box “Patient Education for Herpes Simplex Labialis.” Patients should be advised that the disorder is self-limiting, and that pharmacologic therapy with appropriate agents can keep the affected tissue moist and supple, decrease the itching and pain, protect involved skin from secondary bacterial infection, and help reduce the duration of active infection. The action of each recommended product, its proper use, and possible adverse effects also should be explained.

Evaluation of Patient Outcomes for Herpes Simplex Labialis

In immunocompetent patients, HSL typically is mild and self-limiting, with healing of lesions within 10–14 days.^{22,23,36,46} If the symptoms have resolved, no further treatment is necessary. However, if the condition worsens (e.g., if pain and itching persist, redness increases, or signs of secondary infection are apparent), referral to the patient’s primary care provider is warranted.

Case 32–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient complains of a burning, itching, tingling feeling on the top of his lip, which he has had for almost 3 weeks. He reports that he has had about 6 cold sores over the past 4 months.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Patient reports that he is under a lot of stress, as he has been studying for his LSATs for the past 4 months.
c. Description of the patient's efforts to relieve the symptoms	He has tried an ice pack to relieve the burning and itching, which works until the ice melts. He has also used Carmex and Blistex, which did help with the pain and discomfort.
d. Patient's identity	William Thanyou
e. Patient's age, gender, height, and weight	22 years, male, 6 ft 1 in., 180 lb
f. Patient's occupation	Law student
g. Patient's dietary habits	Eats a lot of fast food, pasta, and pizza.
h. Patient's sleep habits	Roughly 6 hours nightly
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Seasonal allergies, for which he takes loratidine. Exercise-induced asthma, for which he uses albuterol before exertion.
j. Allergies	NKDA
k. History of other adverse reactions to medications	None

Relevant Evaluation Criteria	Scenario/Model Outcome
I. Other (describe) _____	n/a
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	This patient's signs and symptoms are consistent with recurrent HSL or "cold sore." He seems to be in the prodrome stage, in which a lesion has yet to appear (Table 32-4).
3. Identify exclusions for self-treatment (Figure 32-5).	Increased frequency of breakouts and lesions present for >14 days (Figure 32-4)
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer the patient to an appropriate OHCP. (2) Recommend self-care with a nonprescription product for xerostomia. (3) Recommend self-care until the patient can see an appropriate OHCP. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Mr. Thanyo is not a self-care candidate because he meets two of the exclusion criteria.
6. Describe the recommended therapeutic approach to the patient or caregiver.	Mr. Thanyo should consult an appropriate OHCP for treatment.
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"This option is best because you have these symptoms for 3 weeks and you have had frequent episodes over the past 4 months."
Implement	

Relevant Evaluation Criteria	Scenario/Model Outcome
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	Criterion does not apply in this case.
Solicit follow-up questions from the patient or caregiver.	"Is there something I can use to help with the pain and discomfort until I can see my physician tomorrow?"
Answer the patient's or caregiver's questions.	"Any product containing benzocaine 20% should provide acute relief." (Refer to Table 32-4.)
Follow up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Mr. Thanyo in 1 or 2 days to ensure that he has called or made an appointment with an OHCP.

Key: HCTZ = Hydrochlorothiazide; n/a = not applicable; NKDA = no known drug allergy; OHCP = oral health care provider.

Algorithm: Xerostomia

FIGURE 32-5 Self-care for xerostomia. (Source: [References 46-51.](#))

Patient Education for Herpes Simplex Labialis

The objectives of self-treatment of herpes simplex labialis (cold sores) are (1) to relieve pain and irritation while the sores are healing, (2) to prevent secondary infection, and (3) to prevent spread of the lesions. For most

patients, carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

Nondrug Measures

- Keep labial or extraoral lesions clean by gently washing them with mild soap solutions.
- Wash hands frequently to prevent contaminating the lesions and to avoid spreading the virus.
- Avoid factors believed to delay healing such as stress, local injury, wind exposure, excessive sun exposure, and fatigue.
- If outbreaks are related to sun exposure, always use a lip and face sunscreen with appropriate SPF protection. (See [Chapter 39](#) for further discussion related to SPF.)

Nonprescription Medications

- Use topical anesthetics such as benzocaine or dibucaine to relieve burning, itching, and pain. Do not use benzocaine if you have a history of hypersensitivity to other benzocaine-containing products.
- If using products containing camphor and menthol, make sure that the concentration of camphor does not exceed 3% and that the concentration of menthol does not exceed 1%.
- Do not apply hydrocortisone to the lesions.
- If evidence of secondary bacterial infection is seen, apply a thin layer of triple-antibiotic ointment 3–4 times daily.
- Apply the topical agent docosanol 10% (Abreva Cream) to limit the burning, tingling, and itching sensations. Docosanol 10% also can speed up the healing process, thereby reducing the duration of the symptoms.
- If desired, take an oral nonprescription analgesic (e.g., aspirin or other NSAID, acetaminophen) for additional pain relief.
- Do not hold an aspirin tablet in the mouth or place it on oral lesions. The acetylsalicylic acid can cause a chemical burn and tissue damage.
- These products should be used after meals (3–4 times a day), and the patient should avoid eating or drinking for at least 30 minutes

after application.

When to Seek Medical Attention

- See a primary care provider for any of the following outcomes:
 - The lesions do not heal in 14 days.
 - The lesions recur despite appropriate self-care.
 - The self-treatment measures do not relieve discomfort.
 - Signs or symptoms of systemic illness such as fever, malaise, rash, or swollen lymph glands emerge.
 - Symptoms change or worsen.

Key: NSAID = Nonsteroidal anti-inflammatory drug; SPF = sun protection factor.

Source: [References 26, 29–34](#), and [36–41](#).

Xerostomia

Xerostomia, commonly referred to as *dry mouth*, is a syndrome in which salivary flow is limited or completely arrested. A person with normal salivary flow produces up to 1.5 L of saliva every 24 hours. Between 5.5% and 46% of the population is said to be afflicted with persistent dry mouth.⁴⁶

Pathophysiology of Xerostomia

Patients with certain disease states, including *Sjögren syndrome* (an autoimmune condition in which the salivary glands become partly or completely dysfunctional and the presenting manifestations typically include dry mouth and/or dry eyes), diabetes mellitus, depression, and Crohn's disease, are prone to xerostomia.^{46,47} In addition, radiation therapy of the head and neck can cause atrophy of the salivary glands; in the vast majority of treated patients, irreversible compromise of salivary gland function results. Medications that have anticholinergic activity or cause depletion of salivary

flow volume (e.g., antihistamines, decongestants, antihypertensives, diuretics, antidepressants, antipsychotics, sedatives) also can cause xerostomia.^{46,48}

Older patients, who are more likely to be taking multiple medications for chronic diseases, typically are more commonly affected. However, if the xerostomia is drug-induced and the causative medication can be discontinued, normal salivary flow may resume in some cases.⁴⁹⁻⁵¹

Nonpharmacologic causes of xerostomia include the use or consumption of alcohol, tobacco, caffeine, or hot spicy food; blockage of ducts by salivary gland stones (*sialolithiasis*); and mouth breathing.

Clinical Presentation of Xerostomia

Xerostomia can result in difficulty talking and swallowing, stomatitis, burning tongue, and halitosis. Unmoistened food cannot be tasted; therefore, xerostomia can cause loss of appetite with eventual decline in nutritional status.⁴⁶⁻⁴⁸ As a consequence of the decrease in salivary flow and the lack of buffering capacity that saliva provides, the teeth can become hypersensitive.⁴⁶⁻⁴⁸ Xerostomia also can result in an increased incidence of *cervical caries* (decay around the root surfaces of teeth) despite excellent oral hygiene. The inadequacy of salivary flow, which normally washes away food and debris from the teeth, is responsible for this increase in tooth decay.^{46,48} Depending on the status of the patient's dentition, xerostomia can increase the incidence of caries, gingivitis, and more severe periodontal disease or can reduce denture-wearing time. Furthermore, reduced flow of saliva can disturb the balance of microflora species in the oral cavity and predispose affected patients to the development of candidiasis.

Treatment of Xerostomia

Dry mouth should never be discounted as inconsequential. Failure to treat this condition can result in serious complications for some patients.

Treatment Goals

The objectives of self-treatment of xerostomia are (1) to relieve the discomfort of dry mouth, (2) to reduce the risk of dental decay, and (3) to prevent and treat

infections and periodontal disease.

General Treatment Approach

The patient should stop using substances that dry the mouth or erode tooth enamel. If possible, medications that are known to cause xerostomia should be discontinued. To reduce the risk of caries, the patient must maintain good oral hygiene. In mild cases, using sugarless sweets and chewing gums or sucking on ice chips may help to stimulate residual salivary flow.⁴⁸

Commercial artificial saliva products can be used as needed to relieve soft tissue discomfort. [Figure 32–5](#) outlines the self-treatment of xerostomia and lists exclusions for self-care.^{46–49}

Nonpharmacologic Therapy

The patient should avoid exposure to substances that reduce salivation, including tobacco (smoked and smokeless), caffeine, hot spicy foods, and alcohol (including mouth rinses). Medication schedules should be modified in consultation with the treating OHCP to coincide with periods of natural stimulation. For example, patients could take medications that cause dry mouth 1 hour before meals, because eating naturally stimulates an increase in salivary flow. Consequently, the duration of dry mouth would be reduced.

To prevent tooth decay, the xerostomic patient should limit intake of sugary (e.g., candy), starchy (e.g., cookies, potato chips), and acidic foods (e.g., orange juice) that may have been tolerated before but now pose significant danger to oral health.^{49–51} Sugar promotes the bacterial production of acid, which causes tooth decay. Acidic foods also may decrease the pH of saliva, resulting in caries and tooth erosion. Chewing gum sweetened with sugar alcohols (e.g., xylitol), however, may be beneficial. Chewing gum increases salivary flow, and xylitol has not been shown to be cariogenic.^{46–48,50,51} Increasing water intake, especially if it is fluoridated, also will be of benefit. Using a cool mist humidifier at home can help to add moisture in the air, which may provide some level of relief.⁴⁹ Finally, the use of very-soft-bristle toothbrushes will help prevent decay by minimizing tissue abrasion.

Pharmacologic Therapy

Artificial saliva products are the primary agents for relieving the discomfort of dry mouth. They are designed to mimic natural saliva both chemically and physically, and typically these products consist of carboxymethyl or hydroxyethylcellulose solutions with or without fluoride. However, they do not contain the many naturally occurring protective components that are present in innate saliva (digestive and bactericidal enzymes and other naturally occurring proteins). Because these products do not stimulate salivary glands to increase natural saliva production, they must be considered to provide replacement therapy, not a cure for xerostomia. However, such products can be used on an as-needed basis in patients with little or no salivary flow. [Table 32–6](#) lists selected nonprescription saliva substitutes and other xerostomia products. Clinically important drug interactions for xerostomia products are listed in [Table 32–3](#).

TABLE 32–6 Selected Nonprescription Saliva Substitutes and Other Xerostomia Products

Trade Name	Primary Ingredient(s)
ACT Dry Mouth Lozenges	Isomalt, xylitol, glycerin, natural and artificial flavors, sucralose, beta-carotene
Biotene Dry Mouth Oralbalance Gel Biotene Dry Mouth Moisturizing Spray	Glycerin, water, sorbitol, xylitol, carbomer, hydroxyethyl cellulose, sodium hydroxide purified water, glycerin, xylitol, PEG-60 hydrogenated castor oil, VP/VA copolymer, flavor, sodium benzoate, xantan gum, methylparaben, propylparaben, sodium saccharin, cetylpyridinium chloride
Entertainer's Secret Spray	Sodium carboxymethylcellulose; dibasic sodium phosphate; potassium chloride; parabens; aloe vera gel; glycerin
Biotene Dry Mouth Gum	Titanium dioxide, lecithin, xylitol, carnauba wax, sorbitol, resinous glaze, natural and artificial flavor, maltitol syrup, potassium acesulfame, glucose oxidase, lactoperoxidase, potassium thiocyanate, gum base

Key: w/v = Weight per volume.

Source: [Reference 25](#).

Product Selection Guidelines

A majority of artificial saliva products are available as sprays and gels; however, gums and toothpastes also are available. Proper use of a gel involves placing approximately a 1/2-inch length of extruded product onto the tongue and spreading it thoroughly in the mouth. These products can be used at any time; a minimum suggested regimen is after all meals and before going to bed. Products that contain preservatives, such as methyl- or propylparaben, may cause hypersensitivity reactions in certain patients. Patients on low-sodium diets should avoid artificial salivas that contain sodium.

Special Populations

No special considerations are required with use of these products in children (although some products such as Biotene suggest use be targeted to patients 12 years of age or older), pregnant or lactating women, or older adults.²⁷

Assessment of Xerostomia: A Case-Based Approach

The patient should be asked about any history of xerostomia, oral hygiene practices, and regularity of dental care visits. The patient's symptoms should be evaluated to determine whether the condition has progressed to the point that complications are likely. A review of the patient's medical and medication history can identify factors associated with reduced salivation. Furthermore, the interviewing health care provider should determine whether lifestyle or other practices could be contributing to the condition. Asking the patient about concurrent dry eyes or joint symptoms will assess the risk for Sjögren syndrome. Similarly, the assessment should establish whether any salivary gland pain or swelling occurs with eating or after meals, to determine the risk for salivary gland stones.

Patient Counseling for Xerostomia

In general, patients with xerostomia require professional dental management for the condition, in addition to the self-care methods discussed previously and outlined in the box “Patient Education for Xerostomia.” Patients should be encouraged to practice good oral hygiene measures and to see their dentist regularly. In addition, patient counseling should include appropriate information about nonpharmacologic and pharmacologic measures for keeping the oral cavity moist and treating dry mouth, to minimize the increased risk for tooth decay associated with xerostomia. Finally, patient education should highlight signs and symptoms that indicate complications from dry mouth.

Patient Education for Xerostomia

The objectives of self-treatment of xerostomia (dry mouth) are (1) to relieve the discomfort of dry mouth, (2) to reduce the risk of dental decay, and (3) to prevent and treat infections and periodontal disease. For most patients, carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

Nondrug Measures

- To help prevent reduction in salivary flow, avoid use of cigarettes and smokeless tobacco.
- Do not drink or use products that contain alcohol (including mouth rinses) or medications that cause depletion of salivary flow.
- Avoid food or drinks that contain caffeine.
- Avoid hot spicy foods.
- To prevent tooth decay, limit consumption of sugary (e.g., candy), starchy (e.g., cookies, potato chips), and acidic foods (e.g., orange juice). Do not suck on hard candy or lozenges sweetened with sugar.
- If desired, chew gum sweetened with sugar alcohols, such as xylitol, to help increase flow of saliva.

- If possible, take medications 1 hour before meals so that the natural saliva flow caused by food can counteract any mouth dryness.
- To help prevent tooth decay, use a very soft toothbrush to reduce abrasion of the teeth.
- Drink plenty of water especially if it is fluoridated.
- Use a cool mist humidifier at home to help moisten the air.

Nonprescription Medications

- Use artificial saliva products that contain fluoride to relieve the discomfort of dry mouth and to prevent tooth decay.
- If you are on a low-sodium diet, avoid artificial salivas that contain sodium.
- Brush and floss your teeth at least twice daily using a regular toothpaste with fluoride, and see your dentist regularly.

When to Seek Medical Attention

- If your symptoms do not decrease in severity or if they worsen, see a dentist.

Source: [References 46–51](#).

Evaluation of Patient Outcomes for Xerostomia

The patient with xerostomia should return for evaluation after 5–7 days of self-treatment. If the mouth dryness is lessened, the patient should continue using artificial saliva and fluoride products as recommended by an OHCP. The patient also should be advised to continue with nonpharmacologic measures. If the dryness becomes worse or additional symptoms or complications develop, the patient should return to an OHCP for further evaluation.

Key Points for Orofacial Pain and Discomfort

- Tooth hypersensitivity and teething discomfort are not serious and are considered self-treatable problems.
- Self-treatment for toothache should be limited to the temporary relief of pain, because professional dental care is required for complete resolution of the underlying condition.
- RAS is amenable to self-treatment for the relief of pain and irritation so that the lesions can heal, thereby allowing the patient to eat, drink, and perform routine oral hygiene while preventing further complications.
- Minor oral mucosal injury or irritation may be self-treated by controlling discomfort and pain, by using appropriate drug and nondrug measures to aid healing, and by preventing secondary bacterial infection.
- The goals of self-treatment for HSL (cold sores) are to relieve pain and irritation while the sores are healing, to prevent secondary infection, and to prevent spread of the lesions to other areas of the body and to other people.
- Self-treatment of xerostomia (dry mouth) can relieve discomfort from dry mouth, thereby reducing the risk of dental decay as well as preventing and, at times, treating infections.
- If the pain or discomfort worsens or persists after appropriate self-treatment and nondrug measures, medical referral for further treatment is imperative.

Chapter 33: Atopic Dermatitis and Dry Skin

Authors: Kim W. Benner

An estimated one in four persons will seek treatment for a skin disorder in a given year.¹ In the United States, 15%–20% of children and 1%–3% of adults are estimated to have the atopic variant of dermatitis.² Most patients with this chronic skin disorder are believed either to be undertreated or to be self-treating with primarily nonprescription medications.³ Such considerations highlight the need for health care providers to be able to recognize and differentiate among common skin disorders, suggest appropriate treatment, and know when referral to the patient's primary care provider or a dermatologist is warranted.

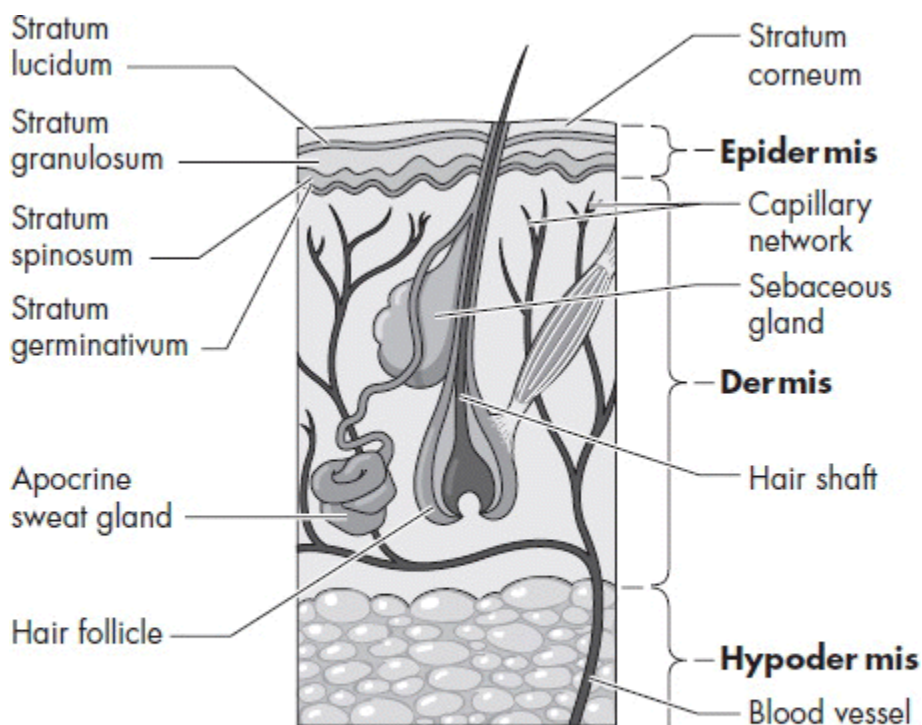
Dermatitis is a nonspecific term for numerous dermatologic disorders that generally are characterized by erythema and inflammation. The designation *eczema* encompasses a group of inflammatory skin disorders that often are of unknown etiology. *Atopic dermatitis* (AD) is a form of eczema in which the skin is chronically scaly, erythematous, edematous, papular, and crusty.⁴ This chapter focuses on AD and dry skin (xerosis), a common accompanying complaint in many dermatoses. Dry skin, which increases in incidence with age, may contribute to decreased quality of life even when of mild to moderate degree, as a consequence of the associated pruritus and, rarely, infection, pain, and inflammation.⁵

Role of Skin in Drug Absorption

An important function of skin and its appendages (hair and nails) is to protect the body from external harmful agents such as pathogenic organisms, ultraviolet solar radiation, and numerous chemicals.⁵ The skin's ability to maintain this protection depends on patient factors of age, immunologic status, and underlying disease states, as well as an intact stratum corneum. Skin also is important in hydroregulation in that it controls moisture loss from the body—specifically, transepidermal water loss (TEWL). If the stratum corneum becomes dehydrated, it loses elasticity and exhibits increased permeability. Despite near-constant exposure to a variety of chemical and environmental insults, the skin demonstrates remarkable resiliency and

recuperative ability.⁶

Human skin has three functionally distinct regions: epidermis, dermis, and hypodermis (Figure 33–1). The epidermis, the outermost, thin layer of the skin, with the *stratum corneum* at its surface, regulates the water content of the skin and controls drug transport into the lower layers and the systemic circulation. The middle layer, the dermis, is 40 times thicker than the epidermis and contains nerve endings, vasculature, and hair follicles. The hypodermis primarily provides nourishment and cushioning for the upper two layers. Skin thickness is variable but averages about 1–2 mm. The thickest skin is on the palms and soles, and the thinnest skin is on the genitalia. These areas with thinner skin areas are more permeable, allowing substances to be absorbed more easily than in areas with thicker skin. As people age, their skin becomes more fragile, requiring a longer recovery time after injury.⁵



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FIGURE 33–1 Cross section of human skin.

A drug applied topically must be released from its vehicle if it is to exert an effect at the desired site of activity (skin surface, epidermis, or dermis). Release occurs at the area of contact between the skin surface and the applied layer of

product. The physical–chemical relationship between the drug and the vehicle determines the rate and amount of drug released. A drug’s solubility in the vehicle, its diffusion coefficient in the vehicle, and its partition coefficient into the sebum and stratum corneum are significant considerations for its efficacy.⁷ The major mechanism of drug absorption is passive diffusion through the stratum corneum, followed by transport through the deeper epidermal regions and then the dermis. The stratum corneum often is the rate-limiting barrier to percutaneous absorption, so its hydration status can affect drug diffusion. Occlusion (blocking or covering an area) increases hydration of the stratum corneum, which enhances the transfer of most drugs. Wounds, burns, and other lesions can alter the integrity of the stratum corneum, with consequent increase in absorption of substances to which it is exposed. Inflammation also can enhance percutaneous absorption of topically applied medications, which may result in higher systemic drug levels.⁷ Therefore, caution is warranted with use of topical medications on compromised skin, particularly if large surface areas are involved.

Atopic Dermatitis

AD is a common, pervasive inflammatory condition of the epidermis and dermis that is characterized by episodic flares and periods of remission. Fifty percent of patients are diagnosed within the first year of life, and as many as 85% present with symptoms before the age of 5 years.² Prevalence of AD worldwide is increasing, possibly because of environmental influences such as climate, urbanization, diet, and pollution/tobacco smoke, but microbial exposure also may be a contributing factor.²

Asthma and allergic rhinitis can occur in up to 80% of patients with AD, emerging either in childhood or with aging.⁸ These three disorders are linked together as the “atopic triad”; a related concept, the “atopic march,” refers to the process whereby infants with AD, via sensitization, are predisposed to the development of asthma and/or allergic rhinitis later in life.⁹ In 80% of cases, AD is classified as mild and can be safely treated with nonprescription products in patients older than 2 years of age.¹⁰ Of note, however, the disorder can place significant social, psychological, and economic burdens on both patients and their families.¹¹ In addition, many persons with AD do not seek medical care for the condition; ultimately, distress over the skin lesions or a flare of symptoms may bring the affected patient or a concerned family member to the local

pharmacy for advice regarding self-care.

Pathophysiology of Atopic Dermatitis

AD is primarily related to two major alterations in the epidermal barrier and the immune system, respectively.¹² Atopic skin is inflamed owing to overexpression of cytokines (the interleukins IL-4 and IL-13) and chemokines produced by T-helper 2 cells.^{12,13} An abundant protein in the epidermal differentiation complex, filaggrin, is related to the development of AD. Thirty-five mutations are known to exist in the filaggrin gene (*FLG*), and presence of even one such mutation increases the risk of AD. The *FLG* mutations can lead to the deficient skin barrier characteristic of AD, including an increased penetration of allergens, a decrease in skin barrier proteins, higher peptidase activity, and lack of protease inhibition. In addition, because of a decreased concentration of lipids, such as ceramides, cholesterol, and fatty acids, atopic skin has an increased TEWL (or a decreased ability to retain moisture).^{5,12,14} The genetic basis for AD is evidenced by definitive diagnosis of the disorder in a patient with a positive family history or in monozygous twins.^{2,15}

AD is diagnosed according to clinical criteria (**Table 33–1**).¹⁶ No established confirmatory laboratory tests are recognized, although elevated immunoglobulin E (IgE) usually is correlated with atopic disease. Patients can have normal total IgE; any elevations in IgE typically do not appear early on and may never occur in some children.^{17,18} Three currently validated disease severity assessments for AD are the SCORAD (SCORing Atopic Dermatitis), EASI (Eczema Area and Severity Index), and POEM (Patient-Oriented Eczema Measure).^{19,20}

TABLE 33–1 Diagnostic Criteria for Atopic Dermatitis

Essential Features

- Pruritus
- Eczema (chronic or relapsing history)

Important Features

- Early age at onset
- Atopy (immunoglobulin E reactivity)
- Xerosis

Note: There are other associated features and exclusionary conditions to consider in diagnosing atopic dermatitis.

Source: [Reference 16](#).

Clinical Presentation of Atopic Dermatitis

AD often manifests within the first year of life, typically by 2–3 months of age. Infantile or childhood AD initially appears as erythema and scaling of the cheeks, which may progress to involve the face, neck, forehead, and extremities (see [Color Plates](#), photographs 16A, B, and C). Crusts and pustules can form from the trauma of scratching and rubbing. Remission can occur by the end of the second year; however, AD and xerosis can continue into adulthood in up to 30% of patients.²¹ AD manifests quite differently in adults than in children and may be less severe in adults.^{14,21} Areas primarily affected in adults include the antecubital and popliteal fossae, neck, forehead, eyes, and hands.²¹ The trigger in adults often is environmental, attributed to chemicals, or skin trauma.²¹

Pruritus, the hallmark symptom of AD, is sometimes referred to as the “itch that rashes.” Patients with AD are more susceptible to pruritus-inducing stimuli. Scratching and repeated rubbing can lead to lichenification (thickened plaques of skin), and excoriations may be seen.²² In all patients, plaques appear erythematous, scaly, exudative, and/or crusty.^{4,23} Of note, atypical presentations are not uncommon, and any undiagnosed skin lesions that persist unchanged over time or that get worse with self-treatment should be evaluated by an appropriate health care provider.

AD has three clinical forms: acute, subacute, and chronic. *Acute AD*, which is characterized by intensely pruritic, erythematous *papules* (small, firm, elevated lesions) or *vesicles* (fluid or air-filled sacs) over erythematous skin, often is associated with excoriation and *serous exudates* (secretions). *Subacute AD* is characterized by erythematous, excoriated papules and *plaques* (large, slightly elevated lesions with a flat surface) that can be scaly. *Chronic AD* is characterized by lichenification and accentuated skin markings.²³

Secondary or associated cutaneous infections, especially bacterial, can be difficult to prevent and typically aggravate the underlying AD. Among patients

with AD-related skin lesions, >90% exhibit lesion colonization with *Staphylococcus aureus* (in contrast with a skin colonization rate of 5% in unaffected persons); streptococci also may be found alone or in association with *S. aureus*.^{9,17,23} Infections manifest as yellowish crusting of the eczematous lesions.⁹

Patients with AD also are susceptible to viral skin infections such as herpes simplex or molluscum contagiosum.^{9,23} True infection of the skin is more common in children with AD, whereas colonization is seen at higher rates in adult patients.²¹ Patients should be counseled to seek medical attention promptly when signs of bacterial or viral skin infection, such as *pustules* (circumscribed, elevated lesions, 1 cm in diameter, containing pus), vesicles (especially those filled with exudate or pus), or crusting, are noticed.²⁴

Treatment of Atopic Dermatitis

Treatment Goals

The goals of self-treatment for AD are (1) to stop the itch–scratch cycle, (2) to maintain skin hydration and barrier function, (3) to avoid or minimize factors that trigger symptoms or aggravate the disorder, and (4) to prevent secondary infections.

General Treatment Approach

At the initial assessment, health care providers should emphasize that AD cannot be cured but that most symptoms can be managed. As in treating any skin condition, nonpharmacologic measures should be attempted first, such as minimization of exposure to factors known to trigger skin irritation. Although only a few new prescription topical agents have been approved for use in AD in the past decade (refer to “Pharmacologic Therapy” section), much has been learned about the pathogenesis of skin barrier changes in AD.^{4,6,12} Enhancing hydration and maintaining the skin barrier in atopic skin can be achieved through nonpharmacologic measures, including the use of moisturizers that can contain emollients (e.g., silicone, oils, or petrolatum, which soften the skin). If pharmacologic therapy is needed, a topical agent should always be the first-line choice. Topical corticosteroids, including hydrocortisone, can relieve itching and inflammation. The algorithm in [Figure 33–2](#) summarizes the approach to self-care for this disorder; exclusions for self-

treatment also are listed.^{9,23}

Nonpharmacologic Therapy

Treatment should be tailored to a patient’s needs and preferences, consistent with the patient’s age, and social conditions, along with the site(s) and severity of the lesions. Education on trigger avoidance and hydration of the skin is of utmost importance in the prevention as well as treatment of AD. Common triggers that patients should avoid are listed in [Table 33–2](#).^{9,15,25} Compared with that of nonaffected persons, the skin of patients with AD may be more reactive to irritants. Accordingly, implementation of preventive measures, with appropriate lifestyle changes, can be expected to reduce symptoms. Such changes include using cotton sheets and clothing, as opposed to wool or other fabrics, which can irritate skin; laundering and thoroughly rinsing new sheets and clothing with unscented or chemical-free laundry detergent; and avoiding fabric softeners. (If fabric softeners are used, liquid products are preferred over dryer sheets.) Bathing can provide hydration and remove bacteria.²⁶ Recommendations for frequency or duration of bathing are lacking, but guidelines state that baths should be limited in duration and taken in lukewarm water without additives.^{27,28} Additionally, moisturizers should be applied immediately after bathing to rehydrate the skin.^{27,28} Because some soaps can be irritating and cause dry skin, mild nonsoap cleansers that are hypoallergenic and fragrance-free (e.g., Cetaphil) are preferred.²⁷

TABLE 33–2 Triggers Associated With Atopic Dermatitis
Food allergens (e.g., egg, milk, peanut, soy, wheat, nuts)
Aeroallergens (e.g., dust mites, cat dander, molds, grass, ragweed, pollen)
Psychological stress
Airborne irritants (tobacco smoke, air pollution, traffic exhaust)
Cosmetics, fragrances, and astringents
Exposure to temperature extremes (heat or cold)
Use of electric blankets
Excessive hand washing or bathing/showering

Use of irritating soaps, detergents, and scrubs
Tight-fitting or irritating clothes (wool or certain synthetics)
Dyes and preservatives

Source: [References 9, 15, and 25.](#)

Although allergens such as plant or animal proteins from food, pollens, or pets are known to aggravate AD, the role of food allergies in exacerbating AD is unclear. It has been previously reported that in about one third of children, food allergies may exacerbate moderate to severe AD.²⁹ These allergies often include sensitivities to egg, milk, peanut, soy, and wheat. Patients with food allergies often have more severe AD, with an earlier onset.²⁸ Children who present with food allergies and AD should be evaluated by an appropriate health care provider, particularly if they are younger than 5 years of age with severe AD.^{10,28} Dietary restriction, especially in children, is difficult to maintain, and although it may produce some symptomatic improvement in AD initially, complete resolution is unlikely. Experts have maintained that patients with moderate to severe AD should eliminate known food allergens.^{9,15,25} However, guidelines state that restriction of offending foods does not alter the risk of developing AD,¹⁶ and note that although food allergies are prevalent in patients with AD, they are not always the cause. Other measures recommended for prevention of AD in childhood, such as breastfeeding and delaying introduction of solid food, remain controversial. Limited studies have investigated these interventions and their role in the prevention of AD; guidelines state that no definite evidence indicates that breastfeeding and solid food introduction will significantly affect risk of development of AD.^{16,28}

Patients with AD often are intolerant of extreme temperatures, as well as sudden and drastic changes in temperature and humidity. High temperatures, by enhancing perspiration, and low humidity, with consequent drying of the skin, both can lead to increased itching. Use of humidifiers in dry environments can provide some benefit.

Pruritus often is bothersome for many patients, who find it difficult to refrain from scratching. Recommending that fingernails be kept short, smooth, and

clean is important to avoid introduction of bacteria through microfissures; in addition, wearing cotton gloves at night can be a helpful preventive measure.

The use of moisturizers is standard of care for AD because maintaining skin hydration and the skin barrier is key to successful management. Moisturizers, especially those containing emollients, should be used at least twice daily for preventive and maintenance therapy to keep skin soft and pliable. The use of natural moisturizing factors, ceramides or pseudoceramides in emollients, can aid in preventing epidermal water loss by means of “barrier repair therapy.”^{6,30} Patient preference should direct specific emollient choice; however, the higher water content in lotions can have a drying effect through evaporation, and their use should be avoided. Ointments may have more effective dermal penetration, but some patients find them unappealingly greasy.^{25,27} Little evidence exists to support one product over the other; therefore, choosing a product that the patient is satisfied with is paramount.^{9,31} Specific information on nonpharmacologic and pharmacologic therapy for AD is presented in the later section “Nonprescription Medications Used to Treat Atopic Dermatitis and Dry Skin.”

Pharmacologic Therapy

Topical corticosteroids are recommended for first-line therapy for AD when nonprescription anti-inflammatory therapy is warranted during acute disease flares.²⁷ Although their exact mechanism of action is unknown, corticosteroids are believed to suppress cytokines involved in the development of inflammation and itching—symptoms that are associated with various dermatoses.

Hydrocortisone, a low-potency corticosteroid, is the nonprescription active ingredient available for self-care. This corticosteroid is safe when used as directed for the short term on virtually any area of the body (including the face, neck, axillae, and groin) and is recognized as safe to use in patients older than 2 years of age.²⁷ Compared with high-potency topical corticosteroid products, hydrocortisone 0.5% and 1% products, when used properly, carry a very low risk of local and systemic adverse effects.^{23,26} Hydrocortisone cream often is the patient-preferred dosage form. Ointment formulations, while often greasy, are preferred for use on areas of thick skin or if the patient’s skin is dry, lichenified, or scaly.^{23,26,32} Hydrocortisone should be applied sparingly twice daily to affected lesions during AD flares, before application of any moisturizers.^{9,27,32}

Ointments should be avoided if the AD lesions are weeping, and all hydrocortisone products should be avoided if the skin is infected, open, or cracked.³³

Topical hydrocortisone rarely produces systemic complications because its systemic absorption in adults is relatively minimal (approximately 1%). Therefore, the risk of adrenal suppression, growth suppression, osteoporosis, and other metabolic complications is slight when low-potency hydrocortisone is used on a short-term basis or rotated with other treatments. Certain local adverse effects such as skin atrophy rarely occur with nonprescription concentrations; they are more common with the more-potent prescription corticosteroids. Intermittent courses of corticosteroids are advised when possible because response to topical hydrocortisone may decrease with continued use. These intermittent courses can include daily use of hydrocortisone only during flares; during remission, use once-or twice weekly dosing, or no hydrocortisone at all, accompanied by continued maintenance strategies such as emollient use.²⁶

Refractory cases of AD necessitate referral to a primary care provider for prescription therapy with a higher-potency topical corticosteroid; a topical calcineurin inhibitor (CNI) (e.g., tacrolimus, pimecrolimus); or a systemic immunomodulator (e.g., cyclosporine, azathioprine, methotrexate).³⁴ Two new prescription agents have recently been approved for AD and provide another promising treatment option for patients with refractory symptoms: Crisaborole is a topical phosphodiesterase inhibitor that was approved for mild to moderate AD in patients >2 years of age. It has a low molecular weight, yielding improved skin penetration, and has proved to be of clinical benefit and safety for up to 48 weeks of use.^{11,35} Dupilumab is an IL-4 receptor antagonist that is approved for adults and children down to 6 years of age with moderate to severe AD.³⁶ This agent is given by subcutaneous injection and has proven efficacy and safety for up to 52 weeks.^{12,13} Because these agents were approved after release of the AD guidelines, their specific place in treatment remains to be established; however, they both offer alternatives to the older agents that are associated with black box warnings (CNIs) or serious adverse events (systemic immunomodulators).

Preventing and managing infections are important in patients with AD because their altered skin barrier predisposes them to such disorders. Guidelines state that the use of topical antibiotics may reduce skin

colonization. However, this effect does not appear to improve patient outcomes, and these products are not routinely recommended.²⁷ Twice-daily diluted bleach baths and intranasal mupirocin have been associated with decreased disease severity and are recommended in moderate to severe AD.^{27,37} Patients should be instructed to prepare a diluted bleach bath by adding ½ cup of bleach per 40 gallons of water (a full bathtub).^{15,25,26}

Although time-consuming for patients and caregivers, the use of “wet wraps” can increase skin hydration and help decrease scratching. This modality entails applying a steroid or emollient to symptomatic lesions, wrapping the affected areas in a wet and then a dry layer, and retaining the wraps for an overnight period.⁹ A growing body of literature is available on the use and efficacy of wet wraps^{38,39}; guidelines recommend their use to decrease disease severity.²⁷

Antipruritics

The pruritus associated with dermatitis may be mediated through several mechanisms, which may explain why local anesthetics, antihistamines, and hydrocortisone all are useful as antipruritics. Older guidelines do not recommend routine use of these local anesthetics (e.g., lidocaine, benzocaine),¹⁵ and newer guidelines do not even mention their potential use.²⁷ Additionally, itching also may be mediated by various endogenous substances, including histamine. On this basis, topical antihistamines (e.g., diphenhydramine) were proposed as agents for alleviating pruritus, with the potential for a cooling effect due to the vehicle.¹⁵ Although topical antihistamines may provide some short-term relief from itching, their use is not recommended and, furthermore, may be associated with sensitization.^{15,27} Oral antihistamines also are not recommended for routine treatment for pruritus in AD because of the lack of demonstrated efficacy and the hypothesis that the pruritus in AD often is not histamine-related.^{15,27} However, an oral antihistamine may help with sleep in the patient who has complaints of insomnia due to excess scratching, and if concurrent depression is a problem, an antidepressant with anticholinergic properties may help further with management of pruritus. In either case, sedation may be a problem, as may the anticholinergic adverse effects in patients with disorders such as benign prostatic hypertrophy or closed-angle glaucoma.⁴⁰ Furthermore, although products marketed as containing “counterirritants” such as menthol, camphor, or capsaicin claim effectiveness, such products are not mentioned in available guidelines.^{15,27}

Complementary Therapies

Although widely used, few complementary therapies have proven benefit in AD. Early research indicated that the use of probiotics in infants, such as *Lactobacillus*, may delay the presentation of AD⁴¹; however, a systematic review revealed no significant difference in AD symptoms.⁴² Published guidelines recommend against the routine use of prebiotics or probiotics for treatment of established AD.⁴⁰ Furthermore, a recent randomized trial provided further evidence of the lack of effectiveness of probiotics for eczema prevention in high-risk infants.⁴³ (Refer to [Chapter 20](#) for more information on probiotics.) The use of phototherapy in patients with AD is of documented benefit and is recommended in the guidelines as second-line therapy for acute and chronic AD.³⁴ Although this agent is not specifically mentioned in the guidelines, some evidence supports the use of topical coconut oil in mild to moderate AD.⁴⁴ Anecdotally, many oils have been utilized by patients for AD; however, the American Academy of Dermatology (AAD) states that there is insufficient evidence to recommend fish, evening primrose, or borage oils; Chinese herbal therapy; and other vitamins/minerals for topical therapy of AD.³⁹ Other natural products used in skin disorders are discussed in [Chapter 51](#).

Algorithm: Self-Care of Dermatitis

FIGURE 33–2 Self-care for dermatitis. Key: ACD = Allergic contact dermatitis; ICD = irritant contact dermatitis; OTC = over-the-counter; PCP = primary care provider.

Dry Skin

Xerosis, or *dry skin*, is the result of decreased water-holding capacity of the skin with resultant alteration of the stratum corneum. Although dry skin can occur at any age, it affects more than 50% of adults older than 65 years. Environmental factors such as temperature extremes and frequent showering can lead to or aggravate dry skin.^{31,45} The prevention of dry skin as well as appropriate skin care for the condition may become a major focus for health care providers as the population of older adults continues to increase.

Pathophysiology of Dry Skin

Dry skin is related to a barrier dysfunction, leading to a decreased water-holding capacity. This barrier dysfunction is due to a decreased amount of lipid components such as ceramides, free fatty acids, and cholesterol, not to a lack of natural skin oils.^{30,46} The decreased water-holding capacity leads to epidermal water loss with consequent dry, cracked skin. Impairment of keratinocyte differentiation also can contribute to the dysfunctional skin barrier.³¹

With advancing age, skin changes occur that include a thinner epithelium, decreasing lipids in the stratum corneum and natural moisturizing factor, and increased susceptibility to drying and bruising. A degraded skin barrier, particularly after insult, is conducive to water loss (and thus xerosis) and a loss of elasticity.^{5,31} Systemic disorders associated with dry skin can include hypothyroidism, cholestasis, renal failure, and dehydration.⁴⁶

Clinical Presentation of Dry Skin

Dry skin is characterized by one or more of the following signs and symptoms: roughness, scaling, cracking, fissuring, and erythema. Affected patients commonly complain of pruritus.^{31,46}

Treatment of Dry Skin

Treatment Goals

The goals of self-treatment for dry skin (xerosis) are (1) to improve skin hydration and minimize water loss, (2) to restore the skin's barrier function, and (3) to educate the patient about prevention and treatment of this chronic disorder.

General Treatment Approach

Treatment involves recognizing the problem as well as modifying the environment and bathing habits to maintain skin hydration. Nonprescription products such as bath oils and moisturizers that contain emollients can aid in moisturizing, softening, and restoring and maintaining barrier function. If needed, topical hydrocortisone can be used to reduce pruritus and erythema.

Nonpharmacologic Therapy

The most important aspects of care are the proper use of moisturizers containing emollients that soften and smooth the skin and modifications to bathing practices. The patient should apply these oil-based emollients immediately after bathing while the skin is damp, with frequent reapplication during the day. Room humidity can be increased with a portable humidifier, or a humidification unit can be added to the home heating system. The patient should be encouraged to stay well hydrated by drinking ample water daily unless contraindicated by any medical disorders. [Table 33–3](#) reviews nonpharmacologic therapy for dry skin.

TABLE 33–3 Nonpharmacologic Therapy of Dry Skin

- Take tub baths with addition of bath oil 2–3 times per week for brief periods (3–5 minutes). Take sponge baths on other days.
- Bathe in tepid water, not more than 3°F above body temperature.
- Within 3 minutes of getting out of the tub, pat the body barely dry, leaving beads of moisture, and generously apply body moisturizer to trap the moisture.
- Apply the body moisturizer at least 3 additional times during the day to the whole body (preferably) or at least to the most affected areas.
- Additional measures include
 - Using corticosteroid ointments rather than creams if short-term use is indicated
 - Maintaining high room humidity

Pharmacologic Therapy

Dry skin is more prone to itching, inflammation, and development of secondary infections. Most moisturizers are mixtures of oils and water, but more severe cases of dry skin may require a product containing a humectant (e.g., glycerin, urea, lactic acid) to enhance hydration. To improve barrier function, agents such as phospholipids and ceramides can be added to these moisturizers. Dry skin responds minimally to topical corticosteroid therapy, although short-term (≤ 7 days) use of topical corticosteroids may reduce symptoms of erythema and pruritus. If resolution does not occur within 1 week, referral for further medical evaluation is warranted because other options may be required for relief of the dry skin.

Nonprescription Medications Used to Treat Atopic

Dermatitis and Dry Skin

Nonprescription medications for dermatitis and dry skin that restore skin hydration include bath products and emollients, which can contain hydrating and keratin-softening agents. Often these ingredients are combined in commonly available nonprescription products (Table 33–4). Many such preparations are available for use on AD lesions or dry skin. These products, reviewed next, can be recommended according to patient preference and therapeutic response.

TABLE 33–4 Selected Nonprescription Dry Skin Products

Primary Ingredient(s)	Trade Name
Petrolatum-Containing Products	
Absorbase Ointment ^a	Petrolatum; mineral oil; ceresin wax; wool wax alcohol; potassium sorbate
AmLactin Cream/Lotion	Ammonium lactate 12%
Aquaphor Ointment	Petrolatum 41%; water
Cetaphil Cream ^a	Petrolatum; glycerin
Cetaphil Gentle Cleansing Bar ^a	Sodium cocoyl isethionate; stearic acid; sodium tallousate; PEG-20; petrolatum
Eucerin Cream ^a	Petrolatum; mineral oil; mineral wax; wool wax alcohol
Jergens Ultra Healing Lotion	Petrolatum; mineral oil; dimethicone; cetearyl alcohol; cetyl alcohol; glycerin
Moisturel Cream/Lotion ^a	Petrolatum; dimethicone; cetyl alcohol; glycerin
Vaseline Intensive Care Advanced Lotion	White petrolatum; mineral oil; dimethicone; glyceryl stearate; cetyl alcohol; glycerin
Ceramide Containing Products	
CeraVe Moisturizing Lotion	Glycerin; ceramide 1, 3, 6, and 11; hyaluronic acid; dimethicone; petrolatum, potassium phosphate

Primary Ingredient(s)	Trade Name
Eucerin Professional Repair Concentrated Lotion	Ceramide 3; glycerin; urea
Counterirritants	
Sarna Anti-Itch Lotion	Camphor 0.5%; menthol 0.5%; carbomer 940; cetyl alcohol; DMDM hydantoin; glyceryl stearate; petrolatum
Miscellaneous Emollients	
Cetaphil Gentle Skin Cleanser Liquid ^a	Cetyl alcohol; stearyl alcohol; PEG
Gold Bond Ultimate Healing Lotion	Glycerin; petrolatum; cetyl alcohol; aloe; cetearyl alcohol; propylene glycol; glyceryl stearate
Keri Original Dry Skin Lotion	Mineral oil; lanolin oil; glyceryl stearate; propylene glycol
Lubriderm Advanced Therapy Lotion	Cetyl alcohol; glycerin; mineral oil; PEG-40; emulsifying wax; vitamin E
Lubriderm Daily Moisturizing Lotion	Mineral oil; petrolatum; sorbitol; lanolin; lanolin alcohol; triethanolamine
Neutrogena Body Oil	Isopropyl myristate; sesame oil
Neutrogena Soap	TEA-stearate; triethanolamine; glycerin
Nivea Body Lotion	Glycerin; mineral oil; isopropyl palmitate; vitamin E; lanolin alcohol
Purpose Gentle Cleansing Bar	Sodium tallowate; sodium cocoate; glycerin; BHT

^a Fragrance-free formulation.

Key: BHT = Butylhydroxytoluene; DMDM = dimethylol dimethyl; PEG = polyethylene glycol; TEA = triethanolamine.

Bath Products

Bath Oils

Bath oils generally consist of a mineral or vegetable oil plus a surfactant. Some commercially available bath oil products include colloidal (ground) oatmeal in

an attempt to provide better relief of itching. Bath oils are minimally effective in improving a dry skin disorder because they are greatly diluted in water. When applied as wet compresses, bath oils (1 teaspoon in $\frac{1}{4}$ cup of warm water) help lubricate dry skin and may allow a decrease in the frequency of full-body bathing. Of note, however, bath oils make the tub and other surfaces slippery, creating a safety hazard, especially for older adults or children.

Cleansers

Typical bath soaps generally contain salts of long-chain fatty acids (commonly oleic, palmitic, or stearic acid) and alkali metals (e.g., sodium, potassium). Combined with water, these products act as surfactants that remove many substances from the skin, including the lipids that normally keep the skin soft and pliable. Glycerin soaps, which are more water-soluble, have a higher oil content than standard soaps because of the addition of castor oil. They are closer to a neutral pH and are regarded as less drying than traditional soaps. Although little objective proof exists to prove their superiority, glycerin soaps are advertised for, and well accepted by, people with skin disorders. Mild cleansers such as Cetaphil or Phisoderm can be recommended if soap is to be avoided.

Moisturizers

Moisturizers are vital in the treatment of AD and dry skin owing to their ability to impart moisture to the skin, thereby increasing skin flexibility. Most moisturizers contain abundant water (60%–80%), which functions as a diluent and evaporates, leaving behind active agents. Emollients, ingredients commonly found in moisturizers, include silicone, dimethicone oils, and petrolatum. These additives function to soften and smooth the skin by filling the space between the desquamating skin scales with oil droplets through which moisture cannot readily escape. The lipid components make the scales on the skin translucent and flatten them against the underlying skin. This flattening eliminates air between the scales and the skin surface, which is partly responsible for a white, scaly appearance.⁶ Unfortunately, this effect is only temporary. However, prudent use of emollients can reduce the incidence of AD, and these agents may be as effective as low-potency topical corticosteroids.⁴

Moisturizers can contain several other components, some of which include

emulsifiers, such as polysorbates and potassium cetyl sulfate, which keep water and lipids in one continuous phase; humectants, such as glycerin, propylene glycol, alpha hydroxy acids, and urea, which help skin retain water; preservatives; fragrance (or none in fragrance-free products); and color (dyes). Specialty additives, such as vitamins (vitamins A, C, D, B complex), which have no known clinical effect, and natural moisturizing factors (e.g., lactate, urea, ammonia, uric acid, glucosamine) also can be added and are reported to regulate the moisture content of the stratum corneum. Owing to the increasing understanding of lipid deficiencies and their relation to barrier dysfunction, lipid ingredients such as ceramides or pseudoceramides are being added to some products to enhance skin barrier protection.^{26,30} Additionally, plant oils derived from avocado, coconut, almond, peanut, safflower, sunflower, olive and others may be included in dry skin products (or used alone), presumably because of their unsaturated fatty acid content, to aid in barrier protection.⁴⁷ Although use of these oils contributes to skin flexibility and lubricity, they are less occlusive than white petrolatum. The differences between moisturizer products often are due to the addition of fragrances, exotic oils, vitamins, protein or amino acid products, and other minor moisturizing aids. Use of such products should be avoided in persons with an allergy to any component.

Vehicle Selection

Moisturizers come in a variety of formulations including butters, gels, oils, ointment, lotions, and creams. In general, creams, ointments, and butters are more difficult to spread, especially in hairy areas (where lotions may be beneficial). *Butters* are stiffer moisturizing formulations sold in jars and often contain shea butter, which is extracted from the nut of the African shea tree. Patients with tree nut allergies appear to be able to use shea butter with minimal risk of an allergic reaction. *Gels* can feel good on the skin because the alcohol component exerts a “cooling” effect, as well as an unwanted drying effect. This component also can cause hypersensitivity in some patients.

Ointments typically are water-in-oil emulsions. Often containing petrolatum, they generally lack consumer appeal because of their greasy texture, difficulty of spreading and removing, and staining properties. The simplest and most economical hand ointment is petroleum jelly, applied at bedtime and covered with wraps or gloves (or socks). To avoid the greasy feeling, patients can gently warm the product in the hands, apply a very thin layer, and massage it into the

skin. Ointments are inappropriate for use with oozing AD lesions because their occlusive effect will not allow the lesions to dry and ultimately heal. Additionally, petrolatum should not be applied over puncture wounds, infected areas, or lacerations because its high-occlusive property may lead to maceration and further inflammation. Application of petrolatum to intertriginous areas (e.g., armpits, groin, perianal region), mucous membranes, and acne-prone areas should be minimized; only a preparation with a low concentration of petrolatum is tolerated in these areas. In addition, ointments may be too occlusive in very warm weather, making creams a better choice.²⁶

Lotions and *creams* typically are oil-in-water emulsions that are less greasy than ointments. These agents help alleviate the pruritus associated with dry skin by virtue of their cooling effect as water evaporates from the skin surface. Lotions may be preferred in milder cases of dryness or in warm weather when the occlusive properties of ointments are an issue.²⁶

Frequency of application depends on the severity of the dry skin disorder and the hydration efficiency of the occlusive agent. Generally, moisturizers should be applied liberally and frequently, or a minimum of 3 times daily, to achieve maximum benefit.²⁷ For dry hands, the patient may need to apply the moisturizing agent after each hand washing, as well as at numerous other times during the day.

Topical Hydrocortisone

Hydrocortisone (0.5% or 1%) is currently the only corticosteroid available without a prescription for the topical treatment of dermatitis in the United States. Although its exact mechanism is unknown, hydrocortisone most likely suppresses cytokines involved in the development of inflammation and itching, which are associated with various dermatoses. U.S. Food and Drug Administration (FDA) monograph indications for use of hydrocortisone in patients older than 2 years include temporary relief of itching associated with minor skin irritations, inflammation, and rashes caused by dermatitis, seborrheic dermatitis, insect bites, poison ivy/oak/sumac dermatitis, soaps, detergents, cosmetics, and jewelry.⁴⁸ Concentrations of 0.5% or 1% are considered appropriate for treating localized dermatitis. Many commercially available nonprescription hydrocortisone products now also contain aloe. (The “Pharmacologic Therapy” section under “Atopic Dermatitis” provides more information on hydrocortisone; also refer to [Chapter 35](#).)

For dry skin of mild degree, a hydrocortisone cream is acceptable; however, an ointment formulation generally provides the best results with chronic, non-oozing dermatoses. Maximizing the application of moisturizers (lotions, creams, ointments) in dry, itchy skin disorders may lessen the required frequency of use of medicated products, such as hydrocortisone.^{21,31}

Product Selection Guidelines

Special Populations

Topical medications are used to treat many common skin disorders in infants and children. Infants have a reduced capability for biotransformation of drugs absorbed by the cutaneous route, owing to an immature hepatic enzyme system. In addition, because the ratio of surface area to body weight in a neonate is approximately two to three times that in an adult, the proportion of drug absorbed per kilogram of body weight is greater in a newborn.⁴⁹ Therefore, patients younger than 1 year should be referred to a primary care provider for the care of skin disorders. Pregnant or lactating patients can be safely treated with topical products if used appropriately. In pregnant patients, any risk to the fetus appears to be low if topical steroids are used in limited quantities and over limited areas of the body.⁵⁰ Use of these agents in pregnancy should be limited to clinical situations in which the potential benefit justifies the potential risk to the fetus; refer to the Preface for a detailed explanation of the pregnancy data. Geriatric patients are more likely to have dry skin owing to age-related skin changes. Bath oils and greasy ointments should be used with caution in older patients because such products can create slippery surfaces, with associated increased risk of falls and/or hindrance of the ability to grasp items, potentially impairing postural stability. Additionally, elderly patients may be at greater risk for the adverse effects of some agents owing to increased absorption through their thinner skin.

Patient Factors and Preferences

When deciding which product to recommend for dermatitis or dry skin, the health care provider must evaluate the active ingredients and the vehicle. Primary active ingredients contained in nonprescription skin products are water and oil. However, a variety of secondary ingredients are added to enhance product “elegance” and stability. Many of these ingredients, such as

preservatives like parabens or benzyl alcohol, have the potential to produce contact dermatitis through either an irritant or a sensitizing effect.³²

The type of vehicle (e.g., ointment, cream, lotion, gel, solution, aerosol) may significantly affect treatment of dermatitis, so product selection should be based on patient preference and location of lesions. Refer to the earlier “Vehicle Selection” section for more information on choosing the appropriate vehicle for each patient. Of note, some novel formulations such as foams, mousses, and gels can be more expensive than traditional creams and ointments. Cases 33–1 and 33–2 are examples of the assessment of patients with dry skin and AD, respectively.

Case 33–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient’s symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient is an older man who presents complaining of patches of red, scaly skin on his hands and legs. He claims he has had these lesions on and off for years. He states that they do occasionally itch but not enough to wake him up at night. He notes that the soles of his feet and palms of his hands are very rough, with some fissures but no open wounds.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient’s symptom(s)	The patient states that the skin symptoms are more bothersome in the winter months and have worsened as he has aged.
c. Description of the patient’s efforts to relieve the symptoms	He has tried using a store-brand unknown “lotion” on the lesions occasionally (“maybe once a week”), with minimal improvement.
d. Patient’s identity	James Smith

e. Patient's age, gender, height, and weight	72 years, male, 5 ft 7 in., 230 lb
f. Patient's occupation	Retired landscaper
g. Patient's dietary habits	"Low carb" diet appropriate for patients with diabetes; drinks black coffee and "a little water."
h. Patient's sleep habits	6–7 hours of sleep per night
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	<i>Hypertension</i> : lisinopril 20 mg once daily; <i>type 2 diabetes</i> : metformin 500 mg twice daily
j. Allergies	No known drug allergies
k. History of other adverse reactions to medications	None
l. Other (describe) _____	Mr. Smith states that he takes long hot tub baths 5–6 times per week. He lives in Madison, Wisconsin, and keeps the temperature in his home at 75 degrees year-round, although he uses a humidifier in his bedroom during the winter months.
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Mr. Smith has dry skin that is most likely caused by environmental factors, in combination with his advancing age.
3. Identify exclusions for self-treatment (Figure 33–2).	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer the patient to his primary care provider or a dermatologist. (2) Recommend self-care with nonprescription moisturizers and nondrug measures. (3) Recommend appropriate self-care until the

	patient can see an appropriate health care provider. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Mr. Smith should begin using a nonprescription moisturizer, in a regimen of at least twice-daily applications of white petrolatum or a moisturizing cream to affected areas. If intense itching is troublesome, nonprescription hydrocortisone 1% cream or ointment may be applied to symptomatic lesions 2 times daily, followed by a moisturizer. (Table 33-3 provides additional information on dry skin therapy.)
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Take brief (3- to 5-minute) full-body baths 2-3 times per week using lukewarm (tepid) water. (Bath oils should be avoided because they make surfaces slippery, increasing the risk of falling.) Pat the skin dry after bathing; apply moisturizer generously. Drink plenty of water daily to help improve skin hydration, and increase the humidity in your home to minimize water loss from the skin."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Dry skin can be managed with nonprescription topical therapy such as moisturizers plus changes in your bathing habits. I see that you have been occasionally using a lotion, but these products can be drying to the skin, so try a cream or ointment instead. If cost is an issue, I can help you pick out a cost-effective agent."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
a. Appropriate dose and frequency of administration	See the box "Patient Education for Atopic Dermatitis and Dry Skin."
b. Maximum number of days	"It is likely the moisturizer will need to be used chronically,

the therapy should be employed	for as long as you have the dry skin lesions. Avoid daily prolonged use (>7 days) of topical hydrocortisone." See the box "Patient Education for Atopic Dermatitis and Dry Skin."
c. Product administration procedures	See the box "Patient Education for Atopic Dermatitis and Dry Skin."
d. Expected time to onset of relief	See the box "Patient Education for Atopic Dermatitis and Dry Skin."
e. Degree of relief that can be reasonably expected	See the box "Patient Education for Atopic Dermatitis and Dry Skin."
f. Most common adverse effects	See the box "Patient Education for Atopic Dermatitis and Dry Skin."
g. Adverse effects that warrant medical intervention should they occur	See the box "Patient Education for Atopic Dermatitis and Dry Skin."
h. Patient options in the event that condition worsens or persists	"If the symptoms get worse or if your lesions, particularly those on the feet, become open, seek assistance from a primary care provider."
i. Product storage requirements	Store in a cool, dry place out of children's reach.
j. Specific nondrug measures	See the box "Patient Education for Atopic Dermatitis and Dry Skin."
Solicit follow-up questions from the patient or caregiver.	"Can I just use my Jergen's Lotion rather than using the Vaseline on my feet and legs?"
Answer the patient's or caregiver's questions.	"Ointments such as Vaseline hold moisture in the skin better than creams or lotions do. Although you may be able to use only your lotion after your skin improves, you would have to apply it 4-5 times daily to achieve the same results that Vaseline will provide."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Ask Mr. Smith to call you to report how his dry skin responded to the recommended therapy, or call him in 1 week to evaluate his response.

Key: ASA = Acetylsalicylic acid; CVD = cardiovascular disease.

Case 33–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient is brought to the community pharmacy by her mother for advice regarding lesions on her face and the tops of her arms. The mother reports that these lesions, which appeared when the patient was about 6 months old, have gotten worse since then despite regular applications of a moisturizing cream. The child seems to scratch the lesions a good deal, but the pruritus does not appear to wake her up at night.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	The mother states that the skin lesions seem to have worsened after introduction of some new solid foods, and she recently changed laundry detergents. The daughter seems to scratch the lesions more often during the winter months.
c. Description of the patient's efforts to relieve the symptoms	The mother has applied a topical moisturizing cream to the patient's lesions for months, but in the winter when the lesions worsened, she also would apply a thin layer of topical hydrocortisone 1% cream once a day, which resulted in some temporary relief.
d. Patient's identity	Julie Taylor
e. Patient's age, gender, height, and weight	23 months, female, 33 inches, 24 lb

f. Patient's occupation	Julie attends daycare 3 mornings per week.
g. Patient's dietary habits	Drinks soy milk; tolerates bland soft table foods.
h. Patient's sleep habits	Sleeps 6 hours per night with 2 naps a day. Mother thinks the itching minimally affects her sleep.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Infant multivitamin once daily
j. Allergies	No known allergies; intolerant to cow's milk
k. History of other adverse reactions to medications	None
l. Other (describe) _____	The family history includes allergies in both parents and asthma in a 5-year-old sibling. The mother reports no tobacco use in the home.
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Patient has lesions consistent with atopic dermatitis (due to lesion description and family history of allergies). They are likely to worsen with continued irritation from scratching.
3. Identify exclusions for self-treatment (Figure 33-2).	Julie is not yet 2 years of age and has lesions on her face.
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer Julie and her mother to her primary care provider/pediatrician, or a dermatologist, for a definitive diagnosis. (2) Recommend an appropriate nonprescription product. (3) Recommend use of an appropriate nonprescription product until Julie can be seen by an appropriate health care provider.

	(4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient or caregiver preferences.	Mrs. Taylor should continue to apply a topical moisturizer cream or ointment to Julie's lesions 3–4 times daily with clean hands. She also should try to keep the lesions and surrounding skin as clean as possible. In addition, Julie should be seen as soon as possible by her primary care provider/pediatrician or a dermatologist. Hydrocortisone should be avoided owing to her age (2 years), unless under the direction of a primary care provider.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Until you can see Julie's pediatrician or other primary care provider or a dermatologist, you should continue to apply a topical moisturizer cream 3–4 times daily to the lesions."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Because of Julie's age and the progression of the lesions despite use of topical therapy, the next step is medical consultation to determine the best treatment options."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	"Try to prevent or discourage Julie from scratching the lesions; putting her in cotton sleep gloves at night may help."
	See the box "Patient Education for Atopic Dermatitis and Dry Skin" for additional information that can be discussed with the primary care provider or dermatologist.
Solicit follow-up questions from the patient or caregiver.	"Are there other nonprescription medications that might help?"
Answer the patient's or caregiver's questions.	"Continual use of a nonprescription topical corticosteroid may assist in lesion clearance, if under the direction of an

	appropriate health care provider. Otherwise, prescription medications are available for treatment of Julie's skin condition as determined by her primary care provider or dermatologist."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Mrs. Taylor in 1-2 days to ensure that she sought further medical care for Julie.

Patient Counseling for Atopic Dermatitis and Dry Skin

Patients with AD should be counseled about achieving control of their disease, the chronic nature of the condition, avoiding exacerbating factors, and appropriate treatment options. The health care provider also should explain factors that cause dry skin and the appropriate measures for restoring barrier function. Finally, the potential for duplications in drug therapy should be addressed; for example, a patient using a nonprescription hydrocortisone product should be advised to stop that medication if a stronger topical corticosteroid is prescribed but to continue using moisturizers. The box "Patient Education for Atopic Dermatitis and Dry Skin" lists specific information to provide in patient counseling.

Evaluation of Patient Outcomes for Atopic Dermatitis and Dry Skin

For patients with AD and dry skin, management should include reevaluation 7 days after initiation of therapy. Visual assessment is the best method of determining treatment response, so a scheduled visit is preferable to a phone consultation. If the symptoms have not abated or have worsened (as evidenced by continued or additional itching, redness, scaling, lesions, or tissue breakdown), medical referral is appropriate.

Patient Education for Atopic Dermatitis and Dry Skin

The primary objectives of self-treatment for atopic dermatitis (AD) are (1) to promote adequate skin hydration, (2) to maintain the skin barrier, (3) to avoid or minimize factors that trigger or aggravate the disorder, and (4) to prevent secondary infections. The primary objective in self-treatment for dry skin—restoring skin moisture and the skin’s barrier function—also can help relieve the discomfort of AD. For most patients, carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes. Understanding that implementing a treatment plan for AD requires patience is key to a successful outcome, because some therapeutic measures can be time-consuming to implement, and often a delay occurs in the time to maximal benefit.

Atopic Dermatitis

Nondrug Measures

- Avoid factors that trigger allergic skin reactions such as clothing or environmental irritants and proven food allergens. Avoid temperature extremes and changes in humidity.
- Take short showers or baths, using lukewarm (tepid) water and a nonsoap cleanser.
- If possible, substitute sponge baths (with tepid water) for full-body bathing.
- Pat skin dry after bath or shower.
- To help prevent injury to the affected area caused by scratching, keep your fingernails short, smooth, and clean. At night, wear cotton gloves or socks on your hands to lessen scratching.

Nonprescription Medications

- Gently wash the affected areas with a nonsoap cleanser before applying topical moisturizers or medication. Apply a moisturizer within 3 minutes after washing while skin is still damp.

- Wash hands before applying any medication.
- Apply a thin layer of nonprescription hydrocortisone 1–2 times daily to dry lesions. Do not use this medication longer than 7 days.
- With proper use of medications and nondrug measures, noticeable improvement can be observed in 24–48 hours.
- Although completely eliminating the rash and itch is possible, the chronic nature of this condition increases the likelihood that lesions could worsen, especially during the winter and summer months.

When to Seek Medical Attention

- If the atopic dermatitis does not improve or worsens after 2–3 days of treatment, consult your primary care provider.

Dry Skin

Nondrug Measures

- Avoid excessive bathing; take brief full-body baths 2–3 times per week, using lukewarm (tepid) water.
- If possible, take sponge baths on other days using lukewarm water to maintain skin hydration.
- Pat dry after bathing or showering.
- Drink plenty of water daily.
- Avoid caffeine and alcohol because they can contribute to dehydration.
- Keep the room humidity higher than normal to minimize evaporation from the skin.
- Moisturizer should be generously applied 3–4 times daily; this regimen should be continued as long as dry skin persists.
- Moisturizers should be applied within 3 minutes after bathing, plus an additional 3 times per day.
- Although complete resolution may be difficult, initial improvement should be seen within 24–48 hours.

Nonprescription Medications

- Apply a moisturizer immediately after bathing while your skin is

damp. Reapply the moisturizer frequently.

- For more severe cases of dry skin, use a product that contains ceramides or pseudoceramides.
- If moisturizers alone do not improve skin lesions, you can apply a thin layer of nonprescription-strength hydrocortisone (before moisturizer) 1–2 times daily to dry lesions. Do not use this medication longer than 7 days.

When to Seek Medical Attention

- If skin dryness worsens after 7 days of treatment, consult a primary care provider.

Key Points for Atopic Dermatitis and Dry Skin

- Most patients with mild to moderate AD or dry skin are candidates for self-treatment with a combination of nonprescription agents and nonpharmacologic modalities.
- Patients with yellow, crusting, eczematous AD lesions and all children younger than 1 year of age with AD require referral to a primary care provider/dermatologist for evaluation and treatment.
- Assessment of patients presenting with dry or eczematous skin lesions should ascertain any recent changes in exposure to soaps, detergents, fragrances, chemicals, irritants, temperature extremes, allergens, and other triggers, followed by recommendations for avoidance of such triggers.
- Counsel patients with dry skin disorders to take brief baths, use lukewarm water, pat dry, and apply moisturizers within 3 minutes of completing the bath or shower.
- Advise patients to use mild skin cleansers and to apply moisturizers at least two times daily.

- Educate the patient with chronic dry skin disorders about the importance of stopping the itch–scratch cycle and maintaining adequate hydration.
- Advise patients to use ointment-based products, whenever possible, to maximize the hydrating benefit. Cream-based products can be recommended for patients who will not comply with use of ointments or for patients with weeping lesions.
- Instruct patients how to properly apply topical hydrocortisone products, using the smallest amount possible only on affected lesions and thoroughly rubbing in the product.
- Advise patients with self-treatable symptoms to contact their primary care provider if symptoms worsen or do not abate within 7 days.

Chapter 34: Scaly Dermatoses

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Chronic scaly dermatoses include dandruff, seborrheic dermatitis, and psoriasis. These disorders involve the uppermost layer of skin, the epidermis. Their primary manifestation is scaling of the skin, with inflammation, erythema, and other changes in appearance of variable degree and severity. *Dandruff* is a less inflammatory form of scaly dermatoses, manifested as more of a subtle dermatitis with relatively fine scaling confined to the scalp and, occasionally, mild erythema or inflammation.¹⁻³ *Seborrheic dermatitis*, which affects the scalp, face, and chest (usually the sternum), typically features significant inflammation and erythema; their degree and extent are based on disease severity.² *Psoriasis* is a highly inflammatory skin disorder characterized by raised plaques and adherent thick, silvery white scales.^{1,4}

Use of nonprescription products constitutes appropriate treatment for most cases of dandruff and seborrheic dermatitis. Mild psoriasis may be responsive to nonprescription treatment, but the management of acute exacerbations (“flares”) may require the attention of a knowledgeable health care provider, often a dermatologist.

Dandruff

Dandruff is a mildly inflammatory scalp disorder that results in excessive scalp scaling.^{2,4} It can be a substantial cosmetic concern and is associated with social stigma and concomitant distress.^{3,4} Previously thought to be a separate entity, this disorder represents the milder end of the seborrheic dermatitis spectrum.^{2,5}

Dandruff generally appears around the onset of puberty with the associated increase in sebaceous gland and hormonal activity.^{6,7} Dandruff shows no gender preference, and bald spots typically are dandruff-free. Sebaceous secretions and individual factors such as skin permeability and fatty acid penetration also may play a role.^{7,8} Finally, intrinsic (e.g., psychological stress) and extrinsic (e.g., cold temperatures) factors may affect hormone levels and skin moisture, respectively, to exacerbate dandruff symptoms.⁶ These factors

play a role in damaging the stratum corneum and worsening dandruff.

Pathophysiology of Dandruff

Dandruff is a hyperproliferative epidermal disorder, characterized by an accelerated epidermal cell turnover and abnormal keratinization, resulting in mild inflammation, flaking, and pruritus.^{2,6} This process involves the presence of *Malassezia* yeast, disruption in skin proliferation, differentiation, and barrier function.² The accelerated cell turnover rate is thought to be caused by the irritant effects of fatty acids and cytokines produced by the *Malassezia* fungi.^{2,6,7} With dandruff, crevices occur deep in the stratum corneum, which cause superficial cracking and the development of large flakes.⁹ If the large scales are broken down to smaller units, dandruff becomes less visible.

Clinical Presentation of Dandruff

Scalp scaling, the sloughing of small white or gray loosely bound flakes, is the only visible manifestation of dandruff. The scaling may occur in small patches or may be distributed across the scalp surface. Patients may experience additional, less common symptoms such as scalp pruritus, dryness, tightness, and irritation. Unlike seborrheic dermatitis and psoriasis, dandruff involves minimal inflammation or erythema.^{2,10}

Treatment for Dandruff

Treatment Goals

The goals of self-treatment for dandruff are (1) to reduce the epidermal turnover rate of the scalp skin by reducing the number of *Malassezia* fungi on the scalp, (2) to minimize the cosmetic embarrassment of visible scaling, and (3) to minimize itch.

General Treatment Approach

Routine shampooing with a general-purpose nonmedicated shampoo daily or every other day often is sufficient to control mild to moderate dandruff. If this approach is not effective, the health care provider may recommend nonprescription medicated antidandruff products. Shampoos containing harsh surfactants such as sodium lauryl sulfate or sodium laureth sulfate

should be avoided because of their damaging effects on the stratum corneum.⁶

A cytostatic agent (e.g., pyrithione zinc, selenium sulfide) generally is recommended initially. Contact time is the key to effectiveness of cytostatic medicated shampoos that contain pyrithione zinc or selenium sulfide to suppress the replication of *Malassezia* fungi.^{11,12} The patient should massage the medicated shampoo into the scalp and leave on the hair for 3–5 minutes before rinsing. Repeated rinsing (2–3 times) after the desired contact time is suggested with medicated shampoos that contain selenium sulfide to ensure that a residue is not left on the hair, where it may cause discoloration. The patient should be instructed to use the medicated shampoo daily for 1 week, then 2–3 times weekly for 2–3 weeks, and thereafter once weekly or every other week to control the disorder.¹³ African American patients may benefit from shampooing once weekly and can consult with a dermatologist for product selection.¹⁴ Scalp scrubbers are useful in all patients, especially those with longer hair, to help ensure adequate contact of the medicated shampoo with the scalp.

Alternatively, nonprescription ketoconazole shampoo, an antifungal shampoo that also has anti-*Malassezia* activity, can be used. Shampoos containing coal tar are usually of limited use and reserved for second-line therapy because they may discolor light hair, clothing, and jewelry. These agents reduce scaling by decreasing the turnover rate of scalp cells.^{15,16} A keratolytic shampoo containing salicylic acid or sulfur also may also be used but is of limited efficacy.

The section “Nonprescription Medications Used to Treat Scaly Dermatoses” provides more information on these agents. If dandruff proves resistant to these agents, the patient should be referred to a knowledgeable health care provider or dermatologist for further evaluation.

Seborrheic Dermatitis

Seborrheic dermatitis is a chronic inflammatory disorder that occurs predominantly in the areas of greatest sebaceous gland activity (e.g., scalp, face, chest).^{3,11,17} It commonly manifests as a red, scaly, itchy rash affecting infants (up to 30 months old), adolescents/young adults, and 1%–3% of adults,

more commonly men.^{5,17,18} Typically more severe during the winter and in low-humidity environments, seborrheic dermatitis also may be aggravated by emotional stress.^{17,19} The risk for development of seborrheic dermatitis is increased in states of immunosuppression (e.g., human immunodeficiency virus [HIV] infection, acquired immunodeficiency syndrome [AIDS], antirejection regimen effects after organ transplantation) and in association with chronic neurologic disorders (e.g., Parkinson disease).²⁰⁻²²

Pathophysiology of Seborrheic Dermatitis

Similar to dandruff, seborrheic dermatitis involves *Malassezia* species and accelerated epidermal proliferation. Areas with dense distribution of sebaceous glands are predominantly affected and exhibit more inflammation compared with dandruff.^{5,7,20} The characteristic accelerated cell turnover and enhanced sebaceous gland activity give rise to skin changes consisting of prominent yellow, greasy scales with erythema.^{4,5}

Clinical Presentation of Seborrheic Dermatitis

Seborrheic dermatitis can manifest in a variety of forms based on its severity and body areas affected. It can involve the scalp, eyebrows, glabella, eyelid margins, cheeks, paranasal areas, nasolabial folds, beard area, presternal area, central back, and retroauricular creases, and typical changes may be evident in and about the external ear canal. The usual clinical presentation consists of fairly well-demarcated, dull, yellowish, oily, scaly areas on reddened skin. Pruritus is common.^{1,4}

The infantile form of seborrheic dermatitis, also known as *cradle cap*, is common in the first 3 months of life. The prevalence diminishes significantly by 1 year of age and then gradually over the next few years.²³ In affected infants, thick, white to yellow-brown greasy scales tend to concentrate on the scalp, but the scales can extend across the entire scalp and into the face, neck, trunk, and extremity regions with subsequent redness and inflammation.^{17,19} Children of color may not have the white to yellow scales and can present with hypopigmentation, flaking, and erythema.²⁴

The most common presentation of seborrheic dermatitis in adults is characterized by yellow, greasy scales on the scalp that often extend to the middle third of the face with subsequent eyebrow involvement (see [Color](#)

Plates, photograph 17). Typically, seborrheic dermatitis manifests as greasy, scaling patches or plaques, exudation, and thick crusting. On the face, flaky scales or yellowish scaling patches on red, itchy skin are seen within the eyebrows and on the glabella.^{3,19} Red scaling, fissures, and swelling may be present in the ear canals, around the auditory meatus, in the postauricular region, or under the earlobe. V-shaped areas of the chest and back intertriginous areas, such as the side of the neck, axillae, submammary region, umbilicus, groin, and gluteal crease, also may be involved.^{1,19} Darker-skinned adults may present with hypopigmentation, and erythema may be difficult to see. Arcuate and petaloid lesions are commonly seen along the hairline in this population.²⁴ In adults, the disease is chronic, lasting for years to decades, with periods of improvement in warmer seasons and periods of exacerbation in the colder months.¹⁹

Treatment for Seborrheic Dermatitis

Treatment Goals

The goals of self-treatment for seborrheic dermatitis are (1) to reduce inflammation and the epidermal turnover rate of the scalp skin by reducing the level of *Malassezia* fungi, (2) to minimize or eliminate visible erythema and scaling, and (3) to minimize itch.¹⁷

General Treatment Approach

Because of the inflammatory nature of seborrheic dermatitis, its treatment is similar to but more aggressive than that for dandruff. Patients should be educated that therapy works by controlling the disease rather than by curing it. Therapy is directed at loosening and removal of scales and crusts, inhibiting yeast colonization, controlling secondary infection, and reducing erythema and itching. The scales and crust loosen with the use of topical antifungal agents, which constitutes first-line treatment for seborrheic dermatitis. If the scales are difficult to remove, applying mineral or olive oil and washing with dishwashing liquid may be beneficial.¹³ Because seborrheic dermatitis is a chronic disorder, regular use of medicated shampoos such as pyrithione zinc and selenium sulfide is key. Patients should work the shampoo into the scalp and then leave the lather on the hair and affected areas for 3–5 minutes. Initially, the shampoo should be used daily for the first week or 2; this regimen is then reduced to 2–3 times per week for the next 4 weeks. African American

patients may benefit from foam shampooing once weekly and can consult with a dermatologist for product selection.²⁴

In infants, seborrheic dermatitis usually is self-limited and is treated primarily by gently massaging the scalp with baby oil, followed by the use of a nonmedicated shampoo (e.g., Johnson's Baby Shampoo, Mustela Foam Shampoo) to remove scales.¹ In cases that do not respond to this treatment, the patient should be referred to a pediatrician. Shampooing is the foundation of treatment in adults, regardless of skin lesion location. Once the disorder is controlled, shampoos containing pyrithione zinc, selenium sulfide, or ketoconazole should be used once a week to prevent relapse regardless of age.

If the odor of a medicated shampoo is objectionable, its use can be followed by a more cosmetically acceptable shampoo or conditioner. Topical corticosteroids are not helpful in controlling dandruff; however, these agents are needed more frequently to treat the more significant inflammation in seborrheic dermatitis.¹⁷ Corticosteroid products may be used to manage seborrheic dermatitis whenever erythema persists after therapy with medicated shampoos. Hydrocortisone ointment should be applied no more than twice daily because of the reservoir effect of the stratum corneum, which slowly releases the corticosteroid over time, and potential greasiness. Treatment should continue until symptoms subside but for no more than 7 consecutive days, since seborrheic dermatitis is rarely cured by nonprescription treatment. If the disorder worsens or symptoms persist longer than 7 days, a dermatologist or other knowledgeable health care provider should be consulted.¹²

Psoriasis

Psoriasis is a chronic inflammatory disease estimated to affect approximately 7.5 million Americans.²⁵ Lesions are often localized, but they may become generalized over much of the body surface. Remissions and exacerbations are unpredictable.^{1,26} Approximately 50% of people with psoriasis find that lesions may clear spontaneously and remain clear for varying periods of time.¹⁹ Unrelenting generalized psoriasis may cause enough psychological and physical distress to adversely affect a patient's quality of life.^{26,27}

The incidence of psoriasis is distributed almost equally between men and

women. Obese patients can have a higher incidence. Psoriasis is seen in all races and geographic regions, but the incidence is lower among people living in countries close to the equator and among people of African American, West African, Native American, and Asian descent.^{1,19}

Although the cause of psoriasis is unknown, exacerbations can be triggered by any of the following^{1,19,26,27}:

- Environmental factors such as physical, ultraviolet, and chemical injury
- Various infections (streptococcal infection, HIV infection)
- Prescription drug use (e.g., antimalarials, beta blockers, interferons, lithium, nonsteroidal anti-inflammatory drugs) and withdrawal of systemic corticosteroids
- Emotional and psychological stress
- Use of alcohol and tobacco

Pathophysiology of Psoriasis

Immunologic mechanisms such as T-cell induction, cytokine production, and keratinocyte and epidermal proliferation are believed to contribute to the development and exacerbation of psoriasis. A genetic predisposition is associated with early-onset disease and first-degree familial history.²⁷

Epidermal cell turnover rate is approximately 8 times shorter in psoriatic skin than in normal skin.²⁸ The duration of psoriasis is variable, with spontaneous exacerbations and remissions possible. Lesions may last a lifetime or disappear quickly.^{19,26}

Clinical Presentation of Psoriasis

Regardless of the clinical form, psoriasis typically is symmetrical.

Approximately 90% of patients experiencing psoriasis present with psoriasis plaque. Lesions start as small papules, which grow and unite to form plaques. Plaques typically are well demarcated and are covered with a silvery-white scale. Plaques also may be painful or itchy.^{19,26,27} (See [Color Plates](#), photographs 18A, B, C.) Common sites for psoriasis plaques are the extensor surfaces of the elbows and knees, lumbar region of the back, scalp, trunk, and genital area. When the scale is lifted from the base of the plaque, punctate bleeding points sometimes are seen within the plaque site (Auspitz sign).^{19,26}

Treatment for Psoriasis

Treatment Goals

The goals of self-treatment for psoriasis are (1) to control or eliminate the signs and symptoms (inflammation, scaling, itching) and (2) to prevent or minimize the likelihood of flares.

General Treatment Approach

Mild cases of psoriasis, characterized by presence of a few localized lesions no larger than a quarter, are amenable to self-treatment with topical agents such as hydrocortisone or emollients. With areas of involvement greater than 5%, facial lesions, or the presence of joint pain, treatment by the patient's primary care provider or a dermatologist with more effective prescription medications and phototherapy will be required.²⁹ In cases not responding to emollients and nonprescription strengths of hydrocortisone or in children younger than 2 years, referral to a knowledgeable health care provider or dermatologist also is warranted.

Numerous nondrug measures can be used by patients in the treatment of psoriasis for both mild and moderate to severe cases. Although these treatments can help relieve symptoms and enhance the local effectiveness of nonprescription and prescription products, such measures alone are unlikely to control the signs and symptoms of the disorder. Patients should avoid physical, chemical, or ultraviolet (UV) trauma to the skin because of the likelihood of development of lesions at the site of skin trauma. Scale removal is an important component of treatment, because scales facilitate the continuation of psoriatic plaques and interfere with the penetration of topical agents.³⁰ Patients with psoriasis should be encouraged to bathe with lubricating bath products (see [Chapter 33](#)) 2–3 times per week using tepid water.³¹

Daily lubrication of the skin after a bath or shower is an essential part of therapy. Emollients moisturize, lubricate, and soothe dry and flaky skin, as well as reduce fissure formation within plaques and help maintain flexibility of the surrounding skin. Pruritic dry skin is common in psoriasis, and emollients and lubricating bath products often provide some relief for this symptom.³² Emollients (e.g., Lubriderm Lotion, Nivea Cream) should be applied to the

lesions within minutes of bathing. To be effective, these products need to be applied liberally with gentle rubbing, up to 4 times daily. Loose scales can be removed by gently rubbing with a soft cloth. Hydrocortisone ointment 1% is the nonprescription medication of choice for treatment of bright red lesions. In some patients, nonprescription treatment may be ineffective and more aggressive treatments may be needed.²⁷

In most cases, psoriasis will not be controlled by nonprescription treatment, and referral to a knowledgeable health care provider or dermatologist will be necessary. In such cases, the selection of therapy must be individualized based on the site, severity, duration, and previous treatment of the disorder, as well as the patient's age. Treatment may be topical, systemic, or a combination of both.

Psoriasis can be controlled but not cured, and remissions do occur. Patients should be educated on controlling the disorder to increase compliance with burdensome and prolonged treatment regimens. In addition, education on understanding and acceptance of the disorder may help reduce the associated emotional stress and the frequency of psychogenic exacerbations. Prevention of flare-ups (flares) should be emphasized. During flares, however, signs and symptoms usually can be controlled adequately using self-care measures, detailed in appropriate patient education and treatment. Flares can be prevented by minimizing known precipitating factors such as emotional stress, skin irritation, and physical trauma.

Management of Scaly Dermatoses

Clinical management of scaly dermatoses (e.g. dandruff, seborrheic dermatitis, and psoriasis) consists of use of various nonprescription medications, for control or eradication of symptoms, with differing mechanisms of action, in combination with self-treatment measures specific to each type of disorder. Appropriate patient counseling and education, as detailed further on, also are essential to optimal clinical outcomes.

Nonprescription Medications Used to Treat Scaly Dermatoses

A variety of products are used to treat or reduce the severity of scaly dermatoses. Hydrocortisone is used to control the inflammation associated

with seborrheic dermatitis and psoriasis. [Table 34–1](#) summarizes the concentrations and indications for currently approved agents,^{19,33} and the algorithm in [Figure 34–1](#) outline self-treatment with these agents.

Table 34–1 Concentrations of Approved Nonprescription Ingredients for Products Used to Treat Scaly Dermatoses			
	Concentration (%)		
Ingredient	Dandruff	Seborrheic Dermatitis	Psoriasis
Coal tar	0.5–5	0.5–5	0.5–5
Hydrocortisone	–	0.5–1	0.5–1
Ketoconazole	1	1	1
Pyridione zinc (brief exposure)	0.3–2	0.95–2	2
Pyridione zinc (residual)	0.1–0.25	0.1–0.25	0.25
Salicylic acid	1.8–3	1.8–3	1.8–3
Selenium sulfide	1	1	1
Sulfur	2–5	2–5	–

Source: [References 19](#) and [33](#)

Patients should shampoo with a nonmedicated, nonresidue regular shampoo to remove dirt, oil, and scales from scalp and hair before using a medicated shampoo. Many shampoos leave a residue on the hair shaft and scalp that may cause local aggravation of the skin changes in scaly dermatoses. Nonresidue shampoos, by contrast, leave the scalp clean and receptive to optimal effects from medicated shampoos. After the nonresidue shampoo is rinsed away, a medicated shampoo is applied and left on the scalp for up to 5 minutes. This treatment regimen can be used daily, if needed, until symptoms are relieved and then 2–3 times weekly.¹²

Cytostatic Agents

Topical cytostatic agents include pyridione zinc, selenium sulfide, and coal tar.

These agents are known to decrease the rate of epidermal cell replication. This curtailment increases the time required for epidermal cell turnover, which in turn allows the possibility of normalizing epidermal differentiation, resulting in a slow decline in visible scales. However, these products have limited efficacy and multiple other detriments that make them poor alternatives.³

Pyrithione Zinc

Pyrithione zinc's mechanism of action is its anti-*Malassezia* activity, which reduces the yeast count in the scalp and skin. Pyrithione zinc binds strongly to both hair and the external skin layers of the scalp, and the extent of binding correlates with clinical performance. The U.S. Food and Drug Administration (FDA) recommends concentrations of 0.3%–2% for treating dandruff and 0.95%–2% for treating seborrheic dermatitis.³⁴ Nonprescription shampoos and soaps are currently available in 1% and 2% concentrations. Pyrithione zinc shampoo is well tolerated when used as directed and is not associated with any major adverse effects. Contact with the eyes should be avoided to prevent stinging.

Selenium Sulfide

Selenium sulfide and pyrithione zinc have a similar mechanism of action.²⁰ As with pyrithione zinc, selenium sulfide is more effective with longer contact time and therefore should be applied in a similar manner.^{11,12} Selenium sulfide must be rinsed from the hair thoroughly; otherwise, discoloration may result, especially with light or dyed hair. Frequent use may leave a residual odor and an oily scalp.

Selenium sulfide is approved in a 1% concentration in nonprescription products to treat dandruff and seborrheic dermatitis.³⁴ A 2.5% lotion formulation is available by prescription for use in resistant cases and other topical fungal infections. The risk of irritation of the mucous membranes and scalp from selenium sulfide is minimal, and no adverse effects are associated with routine use of the 1% shampoo. Contact with the eyelids should be avoided because of the potential for eye irritation.

Coal Tar

For many years, the therapeutic response to coal tar products was believed to be caused solely by its phototoxicity. Now it is believed that coal tar may work

by its ability to cross-link with DNA and arrest excessive skin cell proliferation. Coal tar products have long been popular for treating dandruff, seborrheic dermatitis, and psoriasis. Although many nonprescription products are available, their usefulness is constrained by their potentially unacceptable cosmetic properties and limited clinical efficacy.¹⁵

Coal tar is available in concentrations of 0.5%–5% as creams, ointments, pastes, lotions, bath oils, shampoos, soaps, and gels to self-treat dermatologic disorders.³⁴ This variety of dosage forms is partly the result of attempts to develop a cosmetically acceptable product—one that masks the odor, color, and staining properties of crude coal tar, which most patients find esthetically unappealing.

Adverse effects associated with the use of coal tar include folliculitis (particularly of the axilla and groin), stains to the skin and hair (particularly blond, gray, and dyed hair), photosensitization, and irritant contact dermatitis.³⁵ Rarely, the disorder may worsen on exposure to coal tar products. This possibility is of particular concern in the acute phase of psoriasis, when topical corticosteroids are recommended to reduce inflammation before coal tar preparations are used.³⁵

Coal tar products may be applied to the body, arms, and legs, preferably at bedtime. Because coal tar stains most materials, the patient should use bed linen and clothing for which staining would not present a problem. Overnight application is followed by a bath in the morning to remove residual coal tar and to loosen psoriatic scales. Patients using coal tar preparations should avoid sun exposure for 24 hours after application.

Antifungal Agent

Ketoconazole

Ketoconazole, a synthetic azole antifungal agent, is available as a nonprescription shampoo formulation. Ketoconazole 1% is active against most pathogenic fungi but is indicated specifically for *Malassezia* infections. Patients should use ketoconazole shampoo twice a week for 4 weeks, with at least 3 days between each treatment. Once the disorder is controlled, the shampoo can be applied once weekly to prevent relapse. Adverse effects associated with use of 1% ketoconazole shampoo typically are minimal, but hair loss, skin irritation, abnormal hair texture, and dry skin have been

reported. Patients should be advised to avoid contact of ketoconazole shampoo with the eyes, where it can cause significant irritation.

Keratolytic Agents

The keratolytic agents, salicylic acid and sulfur, can be used in dandruff and seborrheic dermatitis to loosen and lyse keratin aggregates, thereby facilitating their removal from the scalp in smaller particles. These agents act by dissolving the “cement” that holds epidermal cells together. Vehicle composition, contact time, and concentration are important factors in the success of a keratolytic agent. Keratolytic concentrations in nonprescription scalp products are not sufficient to impair the normal skin barrier, but they do affect the abnormal, incompletely keratinized stratum corneum.

Keratolytic agents have a primary, concentration-dependent irritant effect, particularly on mucous membranes and the conjunctiva of the eye. The directions and precautions for the use of keratolytic shampoos are similar to those for ketoconazole shampoo, with the exception that prolonged use (>4 weeks) usually is necessary to obtain a therapeutic response for keratolytics.³⁶

Salicylic Acid

Salicylic acid decreases skin pH, which causes increased hydration of keratin and therefore facilitates its loosening and removal. Topical salicylic acid is useful for psoriasis when thick scales are present. However, application over extensive areas should be avoided because of the potential for percutaneous absorption. Salicylic acid has been approved in concentrations of 1.8%–3% for self-treatment for dandruff, seborrheic dermatitis, and psoriasis.³⁴ One study showed that shampoos containing 1.5% ciclopirox olamine and 3% salicylic acid had efficacy similar to that of 2% ketoconazole shampoo for treatment of dandruff.³⁷ The combination product with ciclopirox is not available in the United States.

Sulfur

Sulfur is believed to cause increased sloughing of cells and to reduce corneocyte counts. Sulfur has been approved in concentrations of 2%–5% to self-treat dandruff only.³⁴ Despite its recognition as a single-entity active ingredient, sulfur often is combined with salicylic acid. Although not an FDA-approved indication, this combination has been commonly used to self-treat

seborrheic dermatitis.²⁶ The use of nonprescription topical preparations containing sulfur has not been associated with any significant adverse effects. **Table 34–2** lists nonprescription products used to treat scaly dermatoses.

Table 34–2 Selected Nonprescription Products to Treat Scaly Dermatoses	
Trade Name	Primary Ingredient(s)
Cytostatic Products^a	
DHS Tar Shampoo; DHS Tar Gel Shampoo; Pentrax Shampoo	Coal tar 0.5%
Head & Shoulders Dandruff Shampoo, Zincon Shampoo	Pyrrithione zinc 1%
DHS Zinc Shampoo, Sebulon Shampoo, ZNP Cleansing Bar	Pyrrithione zinc 2%
Head & Shoulders Clinical Strength Shampoo, Selsun Blue Medicated Treatment Shampoo	Selenium sulfide 1%
Neutrogena T/Gel Shampoo	Tar 2% (equivalent to coal tar 0.5%)
Neutrogena T/Gel Extra Strength Therapeutic Shampoo	Tar 4% (equivalent to coal tar 1%)
Neutrogena T/Derm Body Oil	Tar 5% (equivalent to coal tar 1.2%)
Keratolytic Products	
Sebucare Lotion	Salicylic acid 1.8%
Sebulex Conditioning Shampoo with Protein	Salicylic acid 2%; sulfur 2%
Denorex Extra Strength	Salicylic acid 3%
MG217 Medicated Tar-Free Shampoo	Salicylic acid 3%; sulfur 5%
X-Seb Shampoo	Salicylic acid 4%
Sulfoam Medicated Antidandruff Shampoo, Sul-Ray Dandruff Shampoo	Sulfur 2%
Sul-Ray Cleansing Bar	Sulfur 5%
Antifungal Product	
Nizoral A-D Shampoo	Ketoconazole 1%
Combination Products*	

Trade Name	Primary Ingredient(s)
Neutrogena T/Sal Maximum Strength Therapeutic Shampoo	Salicylic acid 3%; coal tar extract 2%
P&S Plus Gel	Coal tar solution 8%; salicylic acid 2%
Scalpicin Maximum Strength Foam/Solution	Salicylic acid 3%; menthol
Sebutone Shampoo	Coal tar 0.5%; sulfur 2%; salicylic acid 2%
X-Seb Plus Shampoo	Pyrrithione zinc 1%; salicylic acid 2%
X-Seb T Shampoo	Coal tar solution 10%; salicylic acid 4%
X-Seb T Plus Shampoo	Coal tar solution 10%; salicylic acid 3%; menthol 1%

^a Coal tar is not preferred.

Topical Hydrocortisone

Topical hydrocortisone 0.5% and 1% is available without a prescription and is FDA approved for inflammatory skin disorders like scaly dermatoses, which is accompanied by inflammation that is unresponsive to medicated shampoos.^{11,12,19,20} Nonprescription hydrocortisone products can play a role in managing mild psoriasis. Topical corticosteroids have several effects (e.g., anti-inflammatory, vasoconstrictive, immunosuppressive) on cellular activity, which can result in decreased redness and itching. Hydrocortisone ointment is the most potent and effective dosage form. It is preferred in the treatment of psoriasis. Patients should apply the ointment, wait 30 minutes, and then cover the area of the psoriatic plaque with another greasy emollient such as petrolatum to serve as an occlusive dressing.

Adverse effects associated with the use of topical corticosteroids include local atrophy after prolonged use and aggravation of certain cutaneous infections. The possibility of systemic sequelae is enhanced with use of the more potent compounds, use of occlusive dressings, or application to large areas of the

body.

Assessment of Scaly Dermatoses: A Case-Based Approach

Differentiation of the scaly dermatoses involves several factors. The appearance of the scales in the early stages of a disorder is not always definitive. In such cases, the presence and nature of other symptoms and the location of the dermatitis constitute additional important clues in its assessment. Recognition of factors that precipitate or exacerbate the disorder also is helpful in defining the disorder. [Table 34–3](#) describes the distinguishing features of these three dermatoses. Cases 34–1 and 34–2 illustrate the assessment of patients with different scaly dermatoses.

Table 34–3 Distinguishing Features of Scaly Dermatoses			
Feature	Dandruff	Seborrheic Dermatitis	Psoriasis
Location	Scalp	Scalp, face, trunk	Scalp, elbows, knees, trunk, lower extremities
Exacerbating factors	Generally, a stable condition but may be exacerbated by psychological stress, cold temperatures, dry climate	Immunosuppression, neurologic conditions, environmental factors, stress	Environmental factors, infection, medications, stress, alcohol, tobacco
Appearance	Thin, white, or grayish flakes; even distribution on scalp	Macules, patches, and thin plaques of discrete yellow, oily scales on red skin	Discrete symmetrical red plaques with sharp borders; silvery white scales; small bleeding points when scale is removed; difficult to distinguish from seborrhea in early stages or in intertriginous zones
Inflammation	Absent	Present	Present
Epidermal hyperplasia	Absent	Present	Present
Epidermal kinetics	Turnover rate 2 times faster than	Turnover rate about 3 times faster than	Turnover rate about 8 times faster than normal

Feature	Dandruff	Seborrheic Dermatitis	Psoriasis
	normal	normal	

Source: [References 1, 4, 6, 17, 19, 20, 26, and 27](#).

Patient Counseling for Scaly Dermatoses

An important point to convey in patient counseling is that scaly dermatoses are rarely cured by pharmacotherapy; rather, nonprescription agents help control the signs and symptoms of the disorders. Patients also should be advised that fluctuation in severity of seborrheic dermatitis and psoriasis may be related to emotional, physical, or environmental factors.

Explanations of the proper use of antifungal, cytostatic, and keratolytic agents should include information about the contact time of the agent on the affected area(s), possible adverse effects, and signs and symptoms that may indicate a need for medical attention. The box “Patient Education for Dandruff and Seborrheic Dermatitis” and the box “Patient Education for Psoriasis” list specific information to provide in patient counseling for these conditions.

Evaluation of Patient Outcomes for Scaly Dermatoses

Follow-up assessment of the patient’s progress should be done after 1 week of self-treatment. If the symptoms have worsened after this period, the patient should be referred for consultation with a knowledgeable health care provider, such as a dermatologist. If symptoms have not worsened, the patient should return for reassessment after a second week of treatment. If the symptoms persist or have worsened after this period, further medical evaluation is warranted.

Algorithm: Scaly Dermatoses

FIGURE 34–1 Self-care for scaly dermatoses. Key: BSA = Body surface area; OTC = over-the-counter.

Case 34–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient complains of yellow, oily scales along his hairline and around his nose. Some minor erythema also is evident in these areas.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	The condition has grown worse since the onset of cold weather.
c. Description of the patient's efforts to relieve the symptoms	Washing the face twice daily with hand soap has not been proven to be beneficial.
d. Patient's identity	Robert Platt
e. Patient's age, gender, height, and weight	57 years, male, 5 ft 9 in., 185 lb
f. Patient's occupation	Sales manager
g. Patient's dietary habits	Normal healthy diet
h. Patient's sleep habits	6–7 hours per night
i. Concurrent medical conditions, prescription and nonprescription	<i>Depression:</i> sertraline 50 mg daily; <i>hypertension:</i> lisinopril 10 mg daily

Relevant Evaluation Criteria	Scenario/Model Outcome
medications, and dietary supplements	
j. Allergies	NKA
k. History of other adverse reactions to medications	None
l. Other (describe) -----	n/a
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s) (Table 34-3).	Mr. Platt appears to have seborrheic dermatitis on his face. His scalp should be examined closely for involvement as well.
3. Identify exclusions for self-treatment (Figure 34-1).	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Recommend self-care with an appropriate nonprescription product and nondrug measures. (2) Recommend self-care with an appropriate nonprescription product and nondrug measures until Mr. Platt can consult his regular health care provider or a dermatologist. (3) Refer Mr. Platt for further medical evaluation. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into	Nonprescription treatment with pyrithione zinc shampoo can be used initially. Ketoconazole or selenium sulfide shampoo can be recommended if the patient prefers to use an alternative product. Hydrocortisone 1% ointment can be

Relevant Evaluation Criteria	Scenario/Model Outcome
account patient preferences.	applied to reddened areas if 1 week of treatment with medicated shampoo does not resolve redness.
6. Describe the recommended therapeutic approach to the patient or caregiver.	“For the first week, shampoo the hair with the medicated shampoo daily and also use it to wash affected areas of the face. Leave on for 5 minutes; then rinse off. For the next 4 weeks, repeat this procedure only 2–3 times per week. Regardless of the location of the lesions, the hair needs to be regularly shampooed to prevent relapse. Once the condition is controlled, the hair should be shampooed at least once a week to prevent relapse.”
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	“You may use the pyrithione zinc, selenium sulfide, or ketoconazole shampoo according to personal preference and cost.”
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	See the box “Patient Education for Dandruff and Seborrheic Dermatitis.”
Solicit follow-up questions from the patient or caregiver.	“What should I use on my hair on the days I do not use the medicated shampoo?”
Answer the patient’s or caregiver’s questions.	“Any type of nonmedicated shampoo is fine to use. One that does not leave a residue is preferred. Once your condition is controlled, daily use of a shampoo is not necessary unless your scalp is especially oily.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Mr. Platt in 1 week to assess his progress in resolving his seborrheic dermatitis.

Key: n/a = Not applicable; NKA = no known allergies.

Case 34-2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient has had shiny scales bilaterally on her elbows for longer than 6 months. Some minor bleeding occurs when the scales are removed. She now complains of the development of lesions on both of her knees.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	The lesions appeared to worsen after her recent divorce from her husband.
c. Description of the patient's efforts to relieve the symptoms	Use of hydrocortisone 1% cream once daily has been marginally effective. Application of lotion to the lesions is soothing.
d. Patient's identity	Elaine Abel
e. Patient's age, gender, height, and weight	43 years, female, 5 ft 6 in., 195 lb
f. Patient's occupation	Factory line worker
g. Patient's dietary habits	Reports normal diet
h. Patient's sleep habits	Averages 6-8 hours per night.
i. Concurrent medical conditions, prescription and nonprescription	<i>Diabetes</i> , diagnosed 2 years previously: fairly well controlled with metformin 500 mg twice daily;

medications, and dietary supplements	<i>hypothyroidism</i> present for 15 years: well controlled with levothyroxine 100 mcg once daily; <i>allergic rhinitis</i> , present for 20+ years: controlled with loratadine 10 mg once daily
j. Allergies	Penicillin (manifested as rash)
k. History of other adverse reactions to medications	None
l. Other (describe) _____	Mrs. Abel showers once or twice daily.
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s) (Table 34-3).	Mrs. Abel possibly has a flare of psoriasis. The type of lesions and bilateral involvement support this assessment.
3. Identify exclusions for self-treatment (Figure 34-1).	The worsening symptoms and appearance of the lesions on the patient's knees indicate exacerbation of a medical condition that requires more than self-care.
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer Mrs. Abel to her regular health care provider or a dermatologist for definitive diagnosis. (2) Recommend a nonprescription product (hydrocortisone ointment 1% and an appropriate emollient) to use until the appointment for medical evaluation. (3) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Refer the patient to a dermatologist or other knowledgeable health care provider for definitive diagnosis and treatment.
6. Describe the recommended	"Contact your regular health care provider or a

therapeutic approach to the patient or caregiver.	dermatologist to accurately diagnose your condition. Until your appointment, you could switch to applying hydrocortisone ointment 1% to the affected areas 2 times daily. Wait 30 minutes and then liberally apply an emollient.”
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	“You need to see your regular health care provider or dermatologist, because nonprescription therapy won’t be as effective as prescription medications for disease as extensive as yours.”
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	See the box “Patient Education for Psoriasis” for nondrug measures to treat psoriasis.
Solicit follow-up questions from the patient or caregiver.	“I saw on the Internet that treatment with coal tar products is an option for psoriasis. Should I use one of these products?”
Answer the patient’s or caregiver’s questions.	“Although coal tar products have been used for a long time, use of a topical corticosteroid is now considered first-line topical therapy for most patients. The smell and mess associated with using coal tar products are major drawbacks, plus they have limited efficacy.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Call Mrs. Abel in 2 days to ensure that she made an appointment with her regular health care provider or a dermatologist.

Patient Education for Dandruff and Seborrheic Dermatitis

The primary objective of self-treatment for dandruff and seborrheic dermatitis is to reduce the turnover rate of skin cells, which is responsible for the scaly lesions. Controlling inflammation and itching of the affected areas is another treatment objective. Although these disorders are chronic and incurable, carefully following product instructions and the self-care measures can help ensure optimal therapeutic outcomes for many patients.

General Measures

- Nonpharmacologic approaches include avoiding environmental exacerbating factors such as physical trauma, ultraviolet light exposure, and chemical injuries; emotional or psychological stress; or use of alcohol and tobacco.
- Shampoo the hair with the medicated shampoo. Leave the shampoo on the hair for 5 minutes. Then rinse the scalp and face thoroughly.
- Use the shampoo for a minimum of 2 weeks to determine effectiveness; after 4 weeks of use, apply the shampoo once a week to control the condition.
- If you are experiencing persistent itching and inflammation, apply a thin layer of hydrocortisone cream no more than 2 times a day. Wash the affected area(s) before use.
- With use of medication and proper nondrug therapy, noticeable improvement could be observed within 7–14 days. Complete control of the disorder is possible with weekly use of the medicated shampoo. It is likely that exacerbations may occasionally appear, especially during the winter months.
- Stinging or burning may occur if a medicated shampoo enters the eyes.

Dandruff

- Use a medicated shampoo containing pyrithione zinc, selenium sulfide, or ketoconazole. If these agents are ineffective, consult your regular health care provider or a dermatologist. Massage the medicated shampoo into the scalp and leave on the hair for 3–5

minutes before rinsing. Repeated rinsing (2–3 times) after the desired contact time is suggested. Use the shampoo daily for 1 week; then use it 2–3 times weekly for 2–3 weeks, and thereafter once weekly or every other week to control the disorder.

- Coal tar products can be used; however, they have limited efficacy. Coal tar shampoos can stain light hair and cause *folliculitis* (inflammation of hair follicles), dermatitis, and *photosensitization* (sensitivity of the skin to sunlight).
- Keratolytic shampoos also can be used but require longer treatment periods.

Seborrheic Dermatitis

- More aggressive doses of the anti-*Malassezia* shampoos are used for seborrheic dermatitis than for dandruff. Regardless of the location of the lesions, the hair needs to be shampooed. The scalp always has the highest concentration of *Malassezia* yeasts and is the source of the fungus that causes skin lesions. Apply the shampoo to hair, scalp, and any lesions on face, hairline, or body; then massage these areas thoroughly. Use product once daily for 1–2 weeks; then reduce use to 2–3 times a week for the next 4 weeks. Use a medicated shampoo containing ketoconazole, pyrithione zinc, or selenium sulfide. Shampoo the hair and scalp, and apply shampoo directly to any lesions on the face and hairline. Washing the hair at least weekly with a cytostatic agent is absolutely essential to prevent relapses, even when lesions appear only on the face.
- If redness persists after therapy with medicated shampoos, apply hydrocortisone ointment 2 times a day until symptoms subside, and then apply the ointment intermittently to control acute exacerbations. Do not use this agent longer than 7 days. Prolonged use can cause rebound flares when the hydrocortisone is discontinued.

When to Seek Medical Attention

- Consult a knowledgeable health care provider or dermatologist if

clinical improvement does not occur or if the condition worsens after 2 weeks of treatment with nonprescription medications.

Patient Education for Psoriasis

The primary objective of self-treatment for psoriasis is to reduce the turnover rate of skin cells, which is responsible for the scaly lesions. Controlling inflammation and itching of the affected areas and hydrating the skin are other treatment objectives. Although psoriasis is chronic and incurable, carefully following product instructions and self-care measures can help ensure optimal therapeutic outcomes for many patients.

- For itchy, dry skin, use emollients and lubricating bath products (see [Chapter 33](#)). Remove scales by gently rubbing them with a soft cloth after the bath. Do not rub vigorously.
- Prevent flares by minimizing factors that you know are likely to exacerbate the disorder, such as emotional stress, skin irritation, and physical trauma.

When to Seek Medical Attention

- If you have psoriasis lesions plus joint pain, consult a knowledgeable health care provider or a dermatology or rheumatology specialist for treatment.
- Consult your primary care provider or a dermatologist for treatment with prescription products if hydrocortisone ointment and emollients are not effective, the affected area has more than a few lesions, or any lesion is larger than quarter size.
- Consult your primary care provider or a dermatologist if reduction in symptoms does not occur or if the condition worsens after 2 weeks of treatment with nonprescription medications.

Key Points for Scaly Dermatoses

- Mild to moderate scaly dermatoses often can be effectively managed with topical nonprescription products.
- Product selection should be based on the patient's history and previous response to treatment, as well as a careful evaluation of the risks and benefits associated with use of specific nonprescription products.
- A crucial component of management is patient education about the proper application of topical agents, which greatly affects the efficacy of therapy.

Chapter 35: Contact Dermatitis

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Contact dermatitis is a skin disorder characterized by inflammation, redness, and often vesicle and pustule formation, with symptoms of pruritus (itching), burning, and stinging, that develops subsequent to contact with an inciting exogenous substance.^{1,2} The two primary types of contact dermatitis, classified by etiology and presentation, are considered in this chapter. *Irritant contact dermatitis* (ICD) is an inflammatory skin reaction caused by exposure to an irritant substance. *Allergic contact dermatitis* (ACD) is an immunologic skin reaction elicited by an antigen formed in response to contact with an allergenic substance.¹

Contact dermatitis is a major cause of workplace disability.² More than 13 million U.S. workers are potentially exposed to chemicals absorbed through the skin each year.³ According to the U.S. Bureau of Labor Statistics, work-related skin disorders accounted for 18.5% of total workplace injuries in 2017, making occupational skin exposure the second most frequent cause of occupational disorders, with 2.3 cases per 10,000 workers.^{4,5} Overall, contact dermatitis causes 70%–90% of occupational skin diseases, with cosmetologists, cooks, florists, metalworkers, manufacturing workers, and those employed in cleaning, painting, agriculture, health care–related professions, and food service at greatest risk.⁶ Approximately 80% of the cases are ICD.^{2,6} The estimated cost of managing contact dermatitis, which includes treatment and workdays lost, is \$1 billion annually.⁷

Irritant Contact Dermatitis

Persons who frequently wash their hands, handle food, and/or have repeated contact with skin irritants, such as hairstylists and restaurant dishwashers, are at increased risk for development of ICD.^{1,8,9} Substances associated with ICD are listed in [Table 35–1](#). A majority of ICD cases are related to occupation, particularly jobs that involve work with water or exposure to irritant substances. ICD also occurs in the home; however, incidence statistics are available only for exposure associated with employment.

TABLE 35-1 Selected Substances Commonly Associated With Irritant Contact Dermatitis

- Acids, strong (e.g., hydrochloric, nitric, sulfuric, hydrofluoric)
- Alkalis, strong (e.g., sodium, potassium, calcium hydroxides)
- Detergents, soaps, and hand sanitizers
- Epoxy resins
- Ethylene oxide
- Fiberglass
- Flour
- Oils (e.g., cutting, lubricating)
- Oxidants, plasticizers, and activators in athletic shoe components
- Oxidizing agents
- Reducing agents
- Radiation
- Solvents
- Urine and feces
- Water
- Wood dust and products

Source: [References 11](#) and [14](#).

Pathophysiology of Irritant Contact Dermatitis

In most instances, ICD occurs on exposed skin surfaces, such as the face and dorsal surfaces of the hands and forearms. Clinical manifestations may follow a single exposure or develop only after multiple exposures of direct skin contact with a chemical or physical irritant.¹⁰

The three main steps in the pathogenesis of ICD are irritation of and disruption of the skin barrier, stimulation of epidermal cells, and release of proinflammatory cytokines that produce inflammation and skin changes.¹¹ The irritant may be absorbed through the cell membrane, thus destroying cell systems. Destruction to epidermal cells also may be a result of the release of cytokines from chemical exposure.^{1,7} ICD is a non-immune-modulated irritation of the skin by a substance.¹

Several factors may affect the magnitude of the skin response. The presence of existing skin conditions, such as atopic dermatitis, can result in a more profound dermatitis secondary to increased or enhanced permeability of the dermis. The quantity and concentration of substance exposure also affect the

severity of the response. Chemical irritants, acids, and alkalis are likely to produce immediate and severe inflammatory reactions. With mild irritants, such as detergents, soaps, and solvents, repeated exposures often are required before the dermatitis appears. Occlusive clothing and diapers can prolong skin contact with the irritant, promoting greater skin absorption of the irritant and leading to a more severe reaction. In addition, environmental factors such as warmer ambient temperature and higher humidity may contribute to more severe ICD.⁷

Clinical Presentation of Irritant Contact Dermatitis

After exposure to an irritant, the skin becomes inflamed, swells, and turns erythematous. Symptoms often are delayed in onset and generally do not occur immediately after exposure. ICD manifests primarily as dry or macerated, painful, cracked, and inflamed skin. Itching, stinging, and burning commonly accompany the rash. Lesions can develop into bullae, pustules, or coalescing vesicles that are well demarcated and confined to the contact area. The inflammatory reaction varies in severity, ranging from these initial symptoms to ulcer formation and localized necrosis.¹¹ Within days, the dermatitis may crust. If the patient avoids further contact with the irritant, the dermatitis generally resolves in several days.

In patients chronically exposed to an irritant, the affected areas of skin will remain inflamed, may develop fissures and scales, and may become hyper- or hypopigmented.¹ Some patients with chronic ICD recover completely despite continued exposure, whereas others improve but continue to have recurrences. In some cases, chronic exposure to an irritant may lead to necrosis, inflammation, and crusting comparable to or worse than the skin changes observed with the original insult. A finding specific to chronic forms of ICD is *lichenification*, or leathery thickening of the skin.¹

Treatment of Irritant Contact Dermatitis

Treatment Goals

The goals of self-treatment for ICD are (1) to remove the offending agent and to prevent future exposure to the irritant; (2) to provide prompt treatment to

prevent development of chronic dermatitis; (3) to relieve the inflammation, dermal tenderness, and irritation; and (4) to educate the patient on self-management to prevent or treat recurrences.¹²

General Treatment Approach

The primary treatment advice is use of preventive measures to avoid further irritant exposure and appropriate selection and use of therapy. Medical referral is indicated for children younger than 2 years; for patients with involvement of the eyes, eyelids, mouth, face, neck, and genitals; and for patients with dermatitis that involves >10% of the skin's surface. Medical referral also is appropriate when (1) the rash has not decreased in severity within 1 week and (2) chronic dermatitis symptoms are present.

Nonpharmacologic Therapy

Patients should wash the exposed area with copious amounts of lukewarm water and cleanse with a mild or hypoallergenic soap, such as Cetaphil or Dove, to reduce contact time with the irritant and to minimize local symptoms.^{2,13} Patients also can use a saline soak (in a solution of 1 teaspoon of salt dissolved in 1 pint of water) to remove the irritant.¹¹

Pharmacologic Therapy

Removal of the irritant can be achieved by soaking the affected area in Burow's solution (aluminum acetate 5% solution), which has anti-inflammatory, cooling, and antibacterial effects.¹¹ Liberal application of emollients, especially those with high lipid content, to the affected area can restore moisture to the stratum corneum, accelerate regeneration of the skin barrier, and protect the area from further exposure.⁹ Petrolatum is considered the gold standard for prevention of epidermal water loss. Barrier creams can accelerate the rate of healing in damaged skin by promoting increased hydration.¹¹ Colloidal oatmeal baths may help relieve itching.¹

Topical corticosteroids do not target the pathophysiologic process of ICD, and the available evidence is insufficient to support a recommendation for their use in treatment of this condition. Differentiation of ICD from ACD is difficult, however, and these agents may reduce inflammation and relieve itching.¹ Prolonged use has been shown to increase risk for development of ICD.¹¹

Topical caine-type anesthetics and agents commonly found in therapeutic products, including propylene glycol, lactic acid, and salicylic acid, should be avoided because of their ability to cause further skin irritation and potential ACD.¹⁴

Preventive Measures

Irritant exposure can be reduced by using protective clothing, gloves, or other equipment. Frequent changes in coverings can limit the time skin areas are occluded. Routine application of postexposure barrier creams can prevent dermatitis, but the benefit of preexposure application is more questionable.¹⁵ However, an expert panel of dermatologists recommends prophylactic barrier cream application before starting a work period, after washing hands, and after completing a work shift to prevent occupational contact dermatitis.¹⁶ Barrier creams inhibit or delay cutaneous absorption of irritants to reduce effects, but when used alone, they probably do not have a clinically important protective effect. Moisturizers, used alone or in combination with barrier creams, provide a clinically important protective effect for primary prevention of ICD.¹⁷

Water-in-oil emulsions are beneficial against aqueous solutions of irritations, whereas oil-in-water emulsions are beneficial for lipophilic materials. If the irritant is an acid, alkaline, detergent, or water-soluble irritant, a water-repellant barrier cream should be selected.⁹ Oil-repellant type barrier creams are protective against oil, varnishes, and organic solvents. Treatment selection also varies based on acuity of symptoms. With acute ICD, hydrophilic preparations (gel, lotion, or cream) generally are sufficient to provide moisture to the skin barrier, whereas with chronic ICD, water-in-oil-based preparations (i.e., ointments) are more likely to be effective.¹⁷

Despite limited evidence to determine clinical efficacy, emollients, moisturizers, and barrier creams can be recommended to assist in repairing the epidermis and to prevent future exposures.⁸ (See [Chapter 33](#) for more information on these products.) Available evidence supports use of barrier creams for protection against hydrophilic solvents and detergents, but benefit against lipophilic solvents is debatable.⁹ Lipid-rich moisturizers and moisturizers containing urea (in concentrations of 5% or greater) or glycerin in particular also have been shown to be of benefit in ICD.¹² Avoidance of hazardous agents is the best prevention strategy for ICD.¹³

Allergic Contact Dermatitis

Some 3000 chemicals have been cited as substances causing ACD.¹⁸ The most common causes of ACD in the United States are poison ivy, poison oak, and poison sumac, as well as nickel used in jewelry, clothing, and electronics. Nickel is found in some food items, but dermatitis related to nickel generally is localized to areas of contact.^{18,19} Approximately 19% of patients patch-tested for allergies are allergic to nickel, including 11 million children in the United States.^{19,20} Latex allergy is common in health care workers and other frequent wearers of latex gloves, and the latex found in waistbands and sock cuffs also can cause ACD. Fragrances, cosmetics, and skin care products are other common potential allergens.¹⁸ **Table 35–2** lists selected allergenic substances.

TABLE 35–2 Selected Substances Commonly Associated With Allergic Contact Dermatitis

Allergen	Sources
Balsam of Peru	Cough syrups, flavorings
Benzocaine	With sensitivity to caine-type anesthetics, crossover allergy observed with other caine-type local anesthetics, topical medications (for skin, eye, ear), other oral medications
Chromium salts	Potassium dichromate electroplating, cement, leather-tanning agents, detergents, dyes
Cobalt chloride	Cement, metal plating, pigments in paints
Colophony (rosin)	Rosin cake for string instrument bows, sport rosin bags, cosmetics, adhesives
Epoxy resins	Constituents before mixing and hardening
Formaldehyde	Germicides, plastics, clothing, glue, adhesives
Fragrances	Cosmetics, household products, eugenol, cinnamic acid, geraniol, oak moss absolute
Lanolin	Lotions, moisturizers, cosmetics, soaps
Latex	Gloves, syringes, vial closures, elastic waistbands, socks, condoms

Allergen	Sources
Nickel sulfate	In jewelry, blue jean studs, utensils, pigments, coins, tools, many metal alloys encountered daily
Neomycin sulfate	Medications, antibiotic ointments, other aminoglycosides
Plants	<i>Toxicodendron</i> species (poison ivy, oak, sumac), primrose (<i>Primula obconica</i>), tulips, others
Rubber (carba mix)	Added ingredients, accelerators, activators, other processing chemicals
Thimerosal	Preservative in many medications, injectables, cosmetics

Source: [References 1, 14, 18, and 25](#).

Pathophysiology of Allergic Contact Dermatitis

ACD is a delayed hypersensitivity reaction resulting from exposure to a foreign substance that acts as an allergen. Sensitized T cells are activated and migrate to the site of contact to release inflammatory mediators. The rash of ACD ordinarily does not appear on first contact but develops after the exposed person has been previously sensitized to that allergen.¹⁰ ICD often is a precursor to further contact sensitization and subsequent ACD.²¹ The pathophysiologic process leading up to clinical manifestation of the dermatitis consists of several steps: during the induction phase, initial exposure to the antigen sensitizes the immune system. Subsequent contact with the antigen induces a cell-mediated, type IV delayed hypersensitivity reaction, within 24 hours to 21 days. This reaction results in dermatitis and symptoms associated with ACD. In persons previously sensitized, the rash and related symptoms typically appear within 24–48 hours after exposure.^{1,14,18}

Urushiol-Induced Allergic Contact Dermatitis

In the United States, four species of *Toxicodendron* plants belonging to the family Anacardiaceae—Northern or Western poison ivy, Eastern and Western poison oak, and poison sumac—cause dermatoses on exposure ([Table 35–3](#)). As much as 80% of the U.S. population is estimated to be sensitive to urushiol, the

allergic oily sap in these plants. On exposure, urushiol enters the skin within 10 minutes, beginning the sensitization process. Poison ivy/oak/sumac dermatitis has been reported in toddlers, but sensitivity increases into adulthood; of interest, sensitivity appears to be reduced in older persons, but the rash tends to take longer to heal.²²

TABLE 35-3 Toxicodendron Plants Indigenous to North America

Plant	Other Common Names	Common Geographic Location(s)
Poison ivy (<i>Toxicodendron radicans</i>)	Poison vine, mark weed, three-leaved ivy, poor man's liquid amber	Present throughout North America, ranging throughout the United States (Central Plains, Midwest, south central, southeastern, lower Mississippi Valley regions); Canada (Ontario, Nova Scotia); and Mexico
Poison oak, Eastern (<i>Toxicodendron toxicarium</i>)	–	Grows widely in the southeastern United States
Poison oak, Western (<i>Toxicodendron diversilobum</i>)	–	Present throughout the Pacific Coast
Poison sumac (<i>Toxicodendron vernix</i>)	Poison elder, poison ash	Present from Quebec to Florida, primarily in the eastern third of the U.S. coast

Source: [References 24](#) and [25](#).

A person who exhibits sensitivity to one *Toxicodendron* species generally is allergic to all of them. These species are most easily identified as having three leaves emanating from a central stem, with the middle leaflet appearing at the terminal end of the stem. Although “Leaves of three, let it be!” is a helpful warning, some members of the genus differ in the number of leaflets attached to the central stalk.²³

Urushiol is contained and carried within resin canals of the plant. The release

of urushiol occurs only through damage to the plant, either directly by a human agent or from natural causes (e.g., wind, rain, insects, animals).²³ Unwashed, contaminated hands, feet, clothes, or shoes may transfer urushiol to other areas of the body and to other persons. Dermatitis can occur on any skin surface, including the eyes, lips, underarms, buttocks, anus, and genitalia, on contact with or transfer of urushiol.

Poison Ivy

The most common *Toxicodendron* plant found throughout central and northeastern United States and Canada is poison ivy (*Toxicodendron radicans* and *Toxicodendron rydbergii*). The leaves are reddish in the spring, green in the summer, and yellow, orange, or red in the fall. The plant may have greenish-white flowers and whitish-yellow berries. It commonly grows up poles, trees, and buildings, and along roads, hiking trails, streams, dry rocky canyons, and embankment slopes. (See [Color Plates](#), photograph 19A.) *Toxicodendron radicans* is composed of nine subspecies of small shrubs or climbing vines with aerial rootlets. Each leaf has three glossy leaflets with smooth or toothed edges. *Toxicodendron rydbergii* is a dwarf shrub with large, broad, spoon-shaped leaves that have a hairy underside; *T. rydbergii* is the principal variety of poison ivy growing in the northern United States and southern Canada.²³

Poison Oak

Two species of poison oak are indigenous to the United States: *Toxicodendron diversilobum*, which grows in tall clumps or as long vines along the West Coast, and *Toxicodendron toxicarium*, a low-growing shrub found in the eastern and southern areas of the United States. Both species possess leaves similar to those of oak trees, with three fuzzy leaflets per stem. Leaflets edges may be unlobed, lobed, or deeply toothed with rounded tips. The plant may have yellow-white berries. (See [Color Plates](#), photograph 19B.) It is found along streams, in thickets, on wooded slopes, and in dry woodlands. Western poison oak (*T. diversilobum*) may have 3–11 leaflets per stem, with leaves similar to those of California live oak.²⁴

Poison Sumac

Poison sumac (*Toxicodendron vernix*) grows in remote areas of the eastern third and Midwest areas of the United States in bogs and swampy areas. It appears as a tall shrub or small tree, attains a height of roughly 9.8 feet (3 m),

and may resemble an elder or ash tree. Hence, it is also known as “poison elder” and “poison ash.” Its leaves are odd-numbered and pinnate and may be 16 inches (40 cm) long, with 7–13 smooth-edged leaflets that come to a tip. The leaves are orange in the spring, green in the summer, and yellow, orange, or red in the fall. The plant may have greenish-yellow flowers and whitish-green fruits that hang in clusters.^{24,25} (See [Color Plates](#), photograph 19C.)

Clinical Presentation of Allergic Contact Dermatitis

General Presentation

Although ACD and ICD can have similar clinical presentations, ACD is initially distinguished from ICD by the distribution and presentation of the rash, with differentiation more difficult in chronic cases.¹⁵ Furthermore, ACD and ICD often coexist.¹¹ Both ICD and ACD can occur anywhere on the body that is exposed to an irritant, but ICD often is limited to the hands and forearms as a result of occupational exposure. The rash in ACD typically is limited to the area of antigen contact and the immediate surrounding area. Unlike those in ICD, ACD lesions are not well circumscribed and frequently disseminate. For example, reactions to latex gloves involve only the areas covered by the glove and immediately surrounding areas.¹¹ Sensitivity to latex in undergarments occurs in areas of direct contact, such as the waist (in waistbands) or calves (in sock cuffs). The lesions of urushiol-induced ACD, however, often are linear in distribution and/or occur over a broad area, as urushiol may be transferred to other parts of the body from the hands or inanimate objects. ACD generally manifests with papules, small vesicles, and/or bullae over inflamed, swollen skin. Erythema at the site of contact is common. Stronger reactions can include rupture of vesicles, with oozing and weeping and subsequent crust formation.²⁶ Significant itching is a prominent feature of ACD. Chronic forms of ACD may feature lichenification.^{1,14,18}

Presentation of Urushiol-Induced Dermatitis

Symptoms occur only where contact was made with urushiol and begin within a few hours, generally 24–48 hours after contact. The rash does not spread but may appear to do so, as urushiol is absorbed at different rates at different anatomic sites. The affected person also may incur inadvertent repeated

exposure from contaminated objects, clothing, or bed linens or from transfer of urushiol under the fingernails during scratching. Intense itching of exposed skin surfaces is followed by erythema and formation of vesicles or bullae. Presentation depends on patient sensitivity and extent of exposure. The vesicles or bullae may break open, releasing their fluid contents. This fluid does not contain antigenic material and is not a vector for transfer of irritant to other areas of the body or to other people. Patients should be educated that the development of the rash over time in different areas is caused by the response time, skin thickness, and severity of exposure. Oozing and weeping of vesicular fluid generally occur for several days. Papules and plaques may develop in addition to or instead of vesicles and bullae (see [Color Plates](#), photograph 20A). Streaks of vesicles that correspond to the points of urushiol contact from the damaged plant suggest *Toxicodendron* exposure (see [Color Plates](#), photograph 20B). In the last stage of the dermatitis, the affected areas undergo crusting and begin to dry (see [Color Plates](#), photograph 20C).

Severity of Poison Ivy/Oak/Sumac Dermatitis

Mild dermatitis is localized to the unprotected areas of the body that were exposed to the urushiol oil. Linear streaks may be seen, and itching may be minimal. Signs of moderate dermatitis include the appearance of erythema, bullae, papules, and vesicles and inflammation of the exposed skin, in addition to pruritus. Severe dermatitis is distinguished by extensive involvement and edema of the extremities and/or face. Involvement of the eyelids, caused by rubbing them with urushiol-contaminated hands, may occur, with the lids swollen shut in severe cases. Extreme itching, marked irritation and formation of numerous vesicles and bullae may limit daily activities.²⁷ Medical referral for systemic therapy is warranted with dermatitis or edema affecting the eyes, genitalia, face, neck, or large surface areas, as well as secondary infections from scratching.²⁸

Treatment of Allergic Contact Dermatitis

Treatment Goals

The goals of self-treatment for ACD are (1) to remove and avoid further contact with the offending agent; (2) to treat the inflammation; (3) to relieve itching and prevent excessive scratching; (4) to relieve the accumulation of debris from oozing, crusting, and scaling of the vesicle fluids; and (5) to prevent

secondary skin infections.

General Treatment Approach

Because of intense itching and discomfort, the widespread nature of the dermatitis, and/or the magnitude of other symptoms, patients will seek advice on treatment for ACD. Treated or untreated dermatitis will naturally resolve in approximately 10–21 days as a result of defense mechanisms of the patient's own immune system. Topical nonprescription products may be used for symptomatic relief.^{1,29,30} Removing the antigen from the skin as soon as possible may reduce the risk of a full-blown immune reaction and the severity of the immune response (e.g., avoiding jewelry or leather watch bands; switching to latex-free underwear and socks; washing urushiol-contaminated clothes; washing affected areas of the body with mild soap and lukewarm water).

In general, the first several days after the initial appearance of ACD are the most uncomfortable. Treatment depends on the severity of the symptoms from the antigenic reaction ([Figure 35–1](#)). Hydrocortisone 1% cream may be applied to localized areas to reduce inflammation and relieve itching. The cream allows weeping lesions to dry and is preferred over the occlusive ointment for weeping areas. Topical corticosteroids may contain contact sensitizers and can contribute to ACD. This possibility does not rule out use, but ACD secondary to topical corticosteroid ingredients should be considered when the patient does not respond to topical treatment or experiences a flare-up after medication application.³¹ The patient also may use astringent compresses and lukewarm baths to dry oozing vesicles.

Other symptomatic treatment options include use of products containing calamine to assist in drying and colloidal oatmeal baths to relieve itching. Patients should be advised that calamine leaves a visible pink film on the skin, and that colloidal oatmeal makes the bathtub slippery and can clog the drain if residual oatmeal clumps are not removed.

Medical referral is indicated for children younger than 2 years; for patients with involvement of the eyes, eyelids, mouth, and genitals; and for patients with dermatitis that involves more than 20% of the skin's surface when urushiol-induced ACD is suspected.³² For other suspected causes of ACD, dermatitis cases that involve more than 10% of the skin's surface should be referred for

medical evaluation and treatment.³³ Medical referral also is appropriate when (1) signs and symptoms of infection occur (temperature >100.0°F [>37.8°C] or presence of pus or tenderness on the rash); (2) numerous large bullae are present; or (3) the rash has not begun to abate within 1 week.

Nonpharmacologic Therapy

Prevention of Urushiol-Induced Allergic Contact Dermatitis

Patients presenting with ACD should be provided with descriptions and/or photographs of *Toxicodendron* plants. Persons involved in outdoor work or activities should survey the surrounding vegetation to determine the potential risk of exposure and, if needed, take preventive measures. Table 35–4 provides preventive and protective measures, including how to clean contaminated clothing and items. Urushiol may linger on almost any surface for years until it is washed off with soap and water or rubbing alcohol.²⁷

TABLE 35–4 Preventive and Protective Measures for Poison Ivy/Oak/Sumac Dermatitis

Preventive Measures

- Learn the physical characteristics and usual habitat of *Toxicodendron* plants. When outdoors, survey the area to assess potential risk for *Toxicodendron* exposure.
- Cover nose and mouth with a mask and wear protective clothing when eradicating *Toxicodendron* plants near your residence. Mechanically remove the plant and its roots, or apply an herbicide recommended by the state farm bureau or the U.S. Department of Agriculture (USDA) extension services. Do not burn the leaves or roots of *Toxicodendron* plants.

Protective Measures

- Wear protective clothing to cover exposed areas.
- Immediately after exposure, remove and wash clothes with ordinary laundry detergent.
- Wash contaminated clothing separately from noncontaminated clothing.
- Wash bed linens to prevent the transfer of urushiol to other parts of the body.
- Take a shower or wash suspected areas of exposure with soap as soon as possible. Avoid tub baths after initial exposure, because oleoresin may remain in the tub and contaminate body areas that were not originally exposed.
- Clip and meticulously clean fingernails to avoid transferring entrapped urushiol to other skin surfaces.
- If dry cleaning clothes, put contaminated clothing in a plastic bag for transport, and warn facility personnel of possible contamination.
- As soon as possible, thoroughly wash shoes, gloves, jackets or other protective garments,

- sports equipment, garden and work tools, and equipment suspected of carrying urushiol.
- Wear vinyl gloves when washing contaminated objects.
 - Bathe pets after known or suspected exposures to *Toxicodendron* plants.

Source: [References 24](#) and [25](#).

Eradication of Toxicodendron Plants

The eradication of *Toxicodendron* plants may be required when extremely sensitive persons live in close proximity to the plant and its oleoresin. It is essential to cover the nose and mouth with a mask for the eradication process, which should *never* include burning. Patients presenting with *Toxicodendron* ACD in midwinter or during off-season periods may have come in contact with urushiol-contaminated objects. Urushiol remains active within dead and dried parts of plants and on inanimate objects for prolonged periods, sometimes years. It is not unusual for an object to become contaminated with urushiol during the growing season and retain its antigenicity over the winter, causing rashes with each use of the object in succeeding seasons. Apparel including shoes and outerwear, upholstery and carpets, garden and work tools, and recreational and camping equipment such as golf clubs, baseball bats, fishing rods, and tents all have been implicated in such recurrent reactions. Urushiol often is carried into the home or transferred to the person's skin on the fur of pets.^{24,34}

Removal of Antigen at Time of Exposure

Urushiol quickly binds to skin, but it is readily degraded in the presence of water. Washing exposed areas with mild soap and water reduces the risk of transfer and the severity of the rash. Immediate washing is preferred, although washing within 30 minutes of contact may remove urushiol that has not yet entered the dermal layers. Once urushiol has entered the skin and attached to tissue proteins, the antigenic process and reaction begins.^{2,35} Good handwashing technique, including meticulous cleansing under or clipping of the fingernails, is necessary to avoid contaminating additional skin surfaces. Antigen removal methods such as vigorous scrubbing of contaminated skin with a harsh soap or household bleach and use of isopropyl alcohol, hand sanitizers, or other cleansers and organic solvents are not recommended

because they may cause further damage to the skin.

Several products are marketed to wash or cleanse the skin after urushiol exposure. Product prices range widely, and cost should be a consideration in selecting a product. One such product, Zanafel, a poison ivy, oak, and sumac wash (a mixture of alcohol solubles and anionic surfactants), is a topical soap scrub that can be used at any time subsequent to urushiol exposure, even after rash develops, to provide relief from pain and itching. It is intended to prevent or relieve the rash by bonding with urushiol within the dermal layer of the skin to create an aggregate that can be washed away with water.³⁶ Small-cohort studies suggest that Zanafel ameliorates or prevents *Toxicodendron*-induced ACD and reduces the redness and blistering after urushiol exposure, but larger-scale studies are needed to confirm Zanafel's efficacy.^{37,38} Tecnu Original Outdoor Skin Cleanser is another agent formulated for removal of urushiol from the skin to prevent rash and itching. The product contains deodorized mineral spirits, water, propylene glycol, octylphenoxypolyethoxyethanol, mixed fatty acid soap, and fragrance. TEC Labs also markets Tecnu Extreme Medicated Poison Ivy Scrub, which contains the anti-itch ingredient Grindelia robusta 3X.³⁹Table 35–5 provides usage guidelines for these three products.

TABLE 35–5 Usage Guidelines for Products That Remove Urushiol
Zanafel 1. Wet the affected area. 2. Measure 1½ inches of the extruded product into one palm. 3. Wet both hands and rub the product into a paste. 4. Rub both hands on the affected area until complete relief of itching is obtained (for up to 3 minutes). 5. Rinse the affected area thoroughly. 6. If itching returns after several hours, the product may be used again.
Tecnu Original Outdoor Skin Cleanser 1. Apply product to dry, contaminated areas as soon after exposure as possible. 2. Cleanse the treated skin areas by rubbing vigorously for 2 minutes. 3. Wipe away product using a cloth, or rinse off with cool water. 4. Product can be used up to 8 hours after exposure to remove any free oil from the skin. 5. Product also may be used to remove urushiol from objects and pet fur.
Tecnu Extreme Medicated Poison Ivy Scrub

1. Squeeze product into the palm of one hand.
2. Add an equal amount of water to the product and mix.
3. Apply the product to affected skin, and gently rub the area for 15 seconds.
4. Rinse with cool water and gently towel dry.
5. Repeat as needed.

Source: [References 36](#) and [39](#).

A study evaluated the efficacy of three different agents for post-contact rash prevention versus no treatment: a chemical inactivator (Tecnu), a surfactant (Dial Ultra dishwashing soap), and an oil-removing compound (Goop). All three products provided good protection against development of poison ivy rash when used to cleanse skin exposed to urushiol. The difference in protective ability among the products was not significant, but Tecnu had a substantially higher cost.⁴⁰

Relief of Itching

Cold or lukewarm soapless showers temporarily relieve the itching associated with ACD. Hot showers typically intensify itching and may cause scalding or thermal skin injuries to affected areas. Patients may use hypoallergenic soap to maintain cleanliness. Patients should trim fingernails to reduce the risk of secondary bacterial skin infections from scratching.

Pharmacologic Therapy

Pruritus (Itching)

Topical ointments and creams containing anesthetics (e.g., benzocaine), antihistamines (e.g., diphenhydramine), or antibiotics (e.g., neomycin) should not be used for pruritus related to ACD. These agents are known sensitizers and can cause a drug-induced ACD superimposed on the existing ACD.⁴¹ If the patient requires nighttime sedation because of itching, then first-generation oral antihistamines can be used.⁴¹ If itching is not alleviated, referral to a primary care provider for further care may be indicated.

Weeping

Astringents applied to unhealthy serous skin or mucous membranes will decrease weeping, oozing, discharge, or bleeding from dermatitis. They decrease edema, exudation, and inflammation by reducing cell membrane permeability and by hardening the intercellular cement of the capillary epithelium. When applied as a wet dressing or compress, astringents cool and dry the skin through evaporation. They induce vasoconstriction, thereby reducing blood flow in inflamed tissue. In wet dressing form, they also allow cleansing the skin of exudates, crust, and debris. Because astringents generally have low cell penetrability, their activity is limited to the cell surface and interstitial spaces. The protein precipitate that forms may serve as a protective coat, allowing new tissues to grow underneath.

Aluminum acetate solution USP (i.e., Burow's solution) contains approximately 5% aluminum acetate. Its drying ability likely involves complexing of the astringent agent with proteins, thereby altering their ability to swell and hold water. [Table 35–6](#) provides guidelines for preparing and applying Burow's solution to affected areas. In addition to softening and removing crusting, Burow's solution has a mild antipruritic effect.^{[18,42](#)}

TABLE 35–6 Usage Guidelines for Burow's Solution

- Prepare a 1:40 aluminum acetate solution (i.e., Burow's solution) using prepackaged tablets or powder, or add 1–3 tablets or powder packets to 1 pint of cool tap water.
- Stir or shake until fully dissolved.
- Soak affected area 15–30 minutes 3–4 times daily.
- Alternatively, loosely apply a compress to the affected area:
 - Prepare compress by soaking a washcloth, cheesecloth, or small towel in the prepared solution.
 - Gently wring the compress and apply it to the affected area.
 - Rewet and reapply the compress for 20–30 minutes, 4–6 times daily.
- Prepare a fresh container of solution for each soak or application of a compress.

Source: [References 18](#) and [42](#).

Inflammation

Hydrocortisone (0.5% and 1%) is the most effective nonprescription topical agent for treating symptoms of mild to moderate ACD that does not involve edema or extensive areas of the skin. Hydrocortisone is a low-potency corticosteroid capable of vasoconstriction, thereby reducing inflammation and pruritus. It is approved for use in minor skin irritations, itching, and rashes caused by eczema, insect bites, poison ivy, poison oak, poison sumac, soaps, detergents, cosmetics, and jewelry.^{43,44} Urushiol ACD may require a prescription corticosteroid, as the nonprescription strength may be too weak to allow effective treatment of the rash.³² Hydrocortisone is recognized as safe to apply to all parts of the body except the eyes and eyelids. Although systemic absorption is minimal with intact skin, use of topical hydrocortisone over large surface areas, prolonged use, use with an occlusive dressing, or use when skin integrity is compromised can lead to significant systemic absorption. Hydrocortisone cream can be applied as frequently as 3–4 times per day.^{32,43,44}

Generally, topical hydrocortisone is well tolerated, with limited adverse reactions such as a subjective sensation of burning and irritation. Pharmacists should be aware that topical hydrocortisone may rarely cause contact dermatitis.^{44,45} No dressing or bandages should be applied when hydrocortisone is used in self-care treatment. Topical hydrocortisone should not be used in children younger than 2 years of age, except as advised by the family's primary care provider or pediatrician. Other contraindications include persistence of the dermatitis beyond 7 days and reemergence of symptoms a few days after initial clearing, unless the patient is under medical management. When greater than 20% of the body is affected, systemic therapy is recommended, for which referral to an appropriate health care provider is indicated.³²

Product Selection Guidelines

Special Populations

Treatment of contact dermatitis in pediatric patients is similar to the approach used in adults. Emollients, barrier creams, and topical corticosteroids can be used in pediatric patients as described for adults (in accordance with product label instructions). Of note, however, children younger than 8 years of age are more susceptible to systemic absorption of topical pharmacologic agents.¹¹ Use of pharmacologic products in pediatric patients younger than 2 years

without the advice of a pediatrician is discouraged.²⁷

Topical preparations generally are considered safe for use during pregnancy, so long as they are not used for long periods or over extensive areas of the body.⁴⁶ The risk of adverse effects in pregnancy is considered limited with low-potency, topical nonprescription formulations.^{47,48} Other topical preparations (e.g., calamine, colloidal oatmeal, aluminum acetate) are in the “undetermined” pregnancy category. The same precautions described for self-treatment in adults apply in pregnant women. For other treatments, pregnant patients should be referred for medical evaluation. (See the Preface for a detailed explanation of the pregnancy data.)

Older adults should avoid first-generation antihistamines (e.g., diphenhydramine) because of associated sedation and anticholinergic effects. Relief of pruritus should be a primary concern in patients in this age group because of the increased risk for skin damage and infections secondary to scratching. Oatmeal baths and creams and topical hydrocortisone, if used on a small area, can be used to manage itching in these patients.

Patient Preferences

Nonprescription medications for ACD are available in numerous dosage forms. *Creams* are quickly absorbed into the skin, so they allow vesicle fluid to flow freely from blisters and do not trap bacteria. Because a cream is an oil-in-water emulsion, it tends to be drying and is best for use with open weeping lesions. In addition, creams are more cosmetically appealing to patients.⁴⁸ *Gels* offer ease of application and rapid absorption of active ingredients into the skin. Some gels may contain alcohol or similar organic solvents that may cause irritation or burning when applied to open lesions. The use of *ointments* is not recommended when weeping lesions are present. Ointments also should not be applied to open lesions because they may trap bacteria beneath the oleaginous film, potentially leading to secondary infections. *Spray* products are convenient and easily applied to large areas of skin. The use of a spray does not require touching the dermatitis, which could trigger itching. However, aerosol sprays may contain propellants that can cause inflammation and/or alcohol, which causes drying and irritation. [Table 35–7](#) lists specific products to treat poison ivy/oak/sumac dermatitis.

TABLE 35–7 Selected Nonprescription Topical Products for Treatment of Poison Ivy/Oak/Sumac Dermatitis

Trade Name	Primary Ingredient(s)
Aveeno Soothing Bath Treatment	Colloidal oatmeal 100%
Burow's solution	Aluminum acetate 5%
Caladryal Lotion	Calamine 8%; pramoxine hydrochloride 1%
Cortaid Cream	Hydrocortisone cream 1% or 0.5%
Domeboro Astringent Solution Powder Packets	Aluminum sulfate 1347 mg; calcium acetate 952 mg
Ivarest Poison Ivy Itch Spray	Pramoxine HCl 1%, zinc acetate 0.12%

Assessment of Contact Dermatitis: A Case-Based Approach

Circumstances surrounding the emergence of the symptoms and skin changes can help determine the type of dermatitis ([Table 35–8](#)). The main factors that help to distinguish ICD from ACD are (1) history of irritant or allergen exposure, (2) history of known sensitivity on previous exposure, (3) time from exposure (at home, at work, during recreation) to appearance of rash, (4) distribution and appearance of the lesions, (5) severity of symptoms, and (6) improvement of the dermatitis with avoidance of irritants.^{1,2,14,18} Much of the information that distinguishes between ICD and ACD is obtained by taking the patient's history; the distribution and appearance of lesions will be the only factor directly observable at the time of the patient interview. Determining the type and success of previous treatments of similar rashes will aid in selecting appropriate nonprescription medications.

TABLE 35–8 Differentiation of Irritant and Allergic Contact Dermatitis

Symptom or Characteristic	Irritant Contact Dermatitis	Allergic Contact Dermatitis
Itching	Yes, later	Yes, early
Stinging, burning	Early	Late or not at all

Symptom or Characteristic	Irritant Contact Dermatitis	Allergic Contact Dermatitis
Erythema	Yes	Yes
Vesicles, bullae	Rarely or no	Yes
Papules	Rarely or no	Yes
Dermal edema	Yes	Yes
Time to reaction (rash) after exposure	Dependent on irritant	Dependent on antigen
Appearance of symptoms in relation to exposures	Initial or repetitive exposures	Delayed for first exposure; in subsequent exposures, varies according to antigen and sensitivity
Causative substances	Water, urine, flour, detergents, hand sanitizers, soap, alkalis, acids, solvents, salts, surfactants, oxidizers	<i>Toxicodendron</i> plants, fragrances, nickel, latex, benzocaine, neomycin, leather
Substance concentration at exposure	Important	Less important
Mechanism of reaction	Direct tissue damage	Immunologic reaction
Common location	Hands, wrist, forearms, diaper area	Anywhere on body that comes in contact with antigen
Rash/lesions	Demarcated, confined to contact area	Uncircumscribed, frequently disseminate

Source: [References 1, 14, 18, and 19](#).

Cases 35–1 and 35–2 illustrate the assessment of two patients with different presentations of contact dermatitis.

Patient Counseling for Contact Dermatitis

For a patient who presents with possible ICD or ACD but cannot identify contact with irritant chemicals, allergens, or *Toxicodendron* plants, counseling should begin with a review of chemicals or allergens likely to cause dermatitis. Then preventive and protective measures, as well as nonprescription pharmacologic treatment options, should be explained. Information about specific nonprescription agents should include clinical purpose and appropriate use, possible adverse effects, expected time to obtain relief, and signs and symptoms that warrant medical referral for further evaluation. An important self-care consideration is that even though skin may appear normal on initial resolution of the ICD rash, it will take weeks to months for the skin barrier to return to normal, so extra care to protect the skin is necessary.⁴⁹

The box “Patient Education for Contact Dermatitis” lists specific information to provide in patient counseling.

Algorithm: Allergic Contact Dermatitis

FIGURE 35–1 Self-care for contact dermatitis. Key: ACD = Allergic contact dermatitis; ICD = irritant contact dermatitis.

Case 35–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient’s symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature,	The patient is seeking treatment for a rash on both hands and wrists. She has been working as a cosmetologist for 3 years but

Relevant Evaluation Criteria	Scenario/Model Outcome
onset, duration, severity, associated symptoms)	recently changed the brand of products she uses in her salon. She also washes her hands frequently and is exposed to water and chemicals throughout the day. The rash is inflamed, and her skin also is dry and cracked. Upon examination, no vesicles, bullae, open lesions, or signs of infection are evident. Skin changes are limited to the lower arms.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	The problem worsened as she started working longer shifts and stayed booked with more clients. Dryness and itching progressively increased over the past month.
c. Description of the patient's efforts to relieve the symptoms	She tried a "generic lotion" she had on hand, and although it felt soothing upon application, no improvement occurred and the rash persisted.
d. Patient's identity	Stacey Martinez
e. Patient's age, gender, height, and weight	28 years, female, 5 ft 8 in., 150 lb
f. Patient's occupation	Cosmetologist
g. Patient's dietary habits	Normal diet with weekend use of alcohol
h. Patient's sleep habits	Averages 6–7 hours of sleep per night.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	The patient has taken the same oral contraceptive (ethinyl estradiol/levonorgestrel) for the past 6 years. She occasionally uses ibuprofen 400 mg by mouth every 6 hours as needed for headache.
j. Allergies	Amoxicillin (hives)
k. History of other adverse reactions to medications	None
l. Other (describe) -----	n/a
Assess	

Relevant Evaluation Criteria	Scenario/Model Outcome
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Ms. Martinez is suffering from irritant contact dermatitis. The likely source is the chemicals used in hair products and dyes, with excessive hand washing on the job as a background factor.
3. Identify exclusions for self-treatment (Figure 35-1).	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer Ms. Martinez to her primary care provider or a dermatologist. (2) Recommend self-care with a nonprescription product and/or nondrug measures. (3) Recommend self-care until the patient can be seen by an appropriate health care provider. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Ms. Martinez should take protective measures when at work to minimize irritant exposure from hair products and dyes. She should use only mild cleansers, such as Cetaphil, when necessary. She should prophylactically apply a barrier cream every 3-4 hours. She should wear gloves when working with products such as dyes if the glove material is not an additional source of irritation. Emollients such as Aquaphor can be used as well, to increase moisture in the skin.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Completely dry your hands after washing with a mild cleanser such as Cetaphil; then use a hypoallergenic hand cream to provide a barrier against irritants before work and every 3-4 hours. Also, apply an emollient to your hands at bedtime, and cover them with cotton gloves overnight."
7. Explain to the patient or caregiver the rationale for	"Washing and drying your hands will cleanse them of irritants. The hypoallergenic hand cream will relieve dryness. The addition

Relevant Evaluation Criteria	Scenario/Model Outcome
selecting the recommended therapeutic approach from the considered therapeutic alternatives.	of cotton gloves will increase the amount of moisture retained in your skin.”
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
a. Appropriate dose and frequency of administration	See the box “Patient Education for Contact Dermatitis.”
b. Maximum number of days the therapy should be employed	See the box “Patient Education for Contact Dermatitis.”
c. Product administration procedures	See the box “Patient Education for Contact Dermatitis.”
d. Expected time to onset of relief	See the box “Patient Education for Contact Dermatitis.”
e. Degree of relief that can be reasonably expected	“Partial symptomatic relief is likely, because continued exposure cannot be avoided.”
f. Most common adverse effects	See the box “Patient Education for Contact Dermatitis.”
g. Adverse effects that warrant medical intervention should they occur	See the box “Patient Education for Contact Dermatitis.”
h. Patient options in the event that condition	“You should consult a primary care provider if the condition does not improve or if irritation is intolerable.”

Relevant Evaluation Criteria	Scenario/Model Outcome
worsens or persists	
i. Product storage requirements	See the box “Patient Education for Contact Dermatitis.”
j. Specific nondrug measures	See the box “Patient Education for Contact Dermatitis.”
Solicit follow-up questions from the patient or caregiver.	“When should the irritation start to decrease?”
Answer the patient’s or caregiver’s questions.	“You should see a difference in 1 week. If you do not see improvement, contact your primary care provider.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Ask Ms. Martinez to contact you in 1 week and report how the problem responded to the recommended therapy, or call her in 1 week to evaluate her treatment outcome.

Key: n/a = Not applicable.

Case 35–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient’s symptoms and medical history, including	
a. Description of symptom(s) (i.e.,	The patient presents to the pharmacy with intense

Relevant Evaluation Criteria	Scenario/Model Outcome
nature, onset, duration, severity, associated symptoms)	pruritus (itching) on his hands, arms, and lower legs. Vesicles and bullae are present, and some of the vesicles on his arms have extensive oozing. It appears that 20%–25% of his body surface area is affected.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	The itching and skin involvement have gotten worse over the past 48 hours and seem to increase the more the patient scratches to relieve the itching. He has not tried anything other than scratching the affected area when he finds the itching "unbearable." Symptoms began after he pulled some weeds and shrubs on the job.
c. Description of the patient's efforts to relieve the symptoms	Patient reports that no treatment has been used.
d. Patient's identity	James Sullivan
e. Patient's age, gender, height, and weight	25 years, male, 6 ft 1 in., 205 lb
f. Patient's occupation	Landscaper
g. Patient's dietary habits	Normal diet with occasional junk food
h. Patient's sleep habits	The patient sleeps 5–6 hours a night.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	None
j. Allergies	Nickel
k. History of other adverse reactions to medications	Upset stomach with codeine
l. Other (describe) _____	n/a
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Mr. Sullivan is suffering from an allergic contact dermatitis as a result of urushiol exposure from poison ivy. His symptomatology (e.g., redness, swelling, itching,

Relevant Evaluation Criteria	Scenario/Model Outcome
	vesicle and bulla formation) has worsened over time as a result of delayed response to urushiol on different anatomic sites and spread of the irritant through scratching.
3. Identify exclusions for self-treatment (Figure 35-1).	Significant proportion of body surface affected (>20%)
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer Mr. Sullivan to his primary care provider or a dermatologist. (2) Recommend self-care with a nonprescription product and/or nondrug measures. (3) Recommend self-care until Mr. Sullivan can obtain medical attention. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Recommend self-care until Mr. Sullivan can see an appropriate health care provider.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Owing to the extent of skin involvement, your poison ivy dermatitis is likely best treated with an oral corticosteroid prescription from your health care provider. While waiting to get an appointment, you can use topical hydrocortisone 1% cream to reduce itching, an astringent like Burow's solution, and cool or lukewarm showers."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Allergic contact dermatitis from urushiol involving greater than 20% of the body should not be treated with self-care products."

Relevant Evaluation Criteria	Scenario/Model Outcome
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	"Expect some relief within a few hours of application. Complete relief of your symptoms is unlikely with nonprescription products, but they will resolve within 10–21 days regardless of treatment."
Solicit follow-up questions from the patient or caregiver.	"I've heard about Zanfel. I work outside for a living. Should I use that in the future?"
Answer the patient's or caregiver's questions.	"The best approach is to learn how to identify <i>Toxicodendron</i> plants and to wear long layers and gloves when you must work near or with these plants. If you suspect you have been exposed to urushiol, you can use Zanfel or Tecnu irritant cleansers to reduce exposure."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Mr. Sullivan within 2–3 days to ensure that he made an appointment and received medical care.

Key: n/a = Not applicable.

Patient Education for Contact Dermatitis

Irritant Contact Dermatitis

The goals of self-treatment for irritant contact dermatitis (ICD) are (1) to remove the offending agent and to prevent future exposure to the irritant; (2) to provide prompt treatment to prevent development of chronic dermatitis; (3) to relieve the inflammation, dermal tenderness, and irritation; and (4) to educate the patient on self-management to prevent or treat recurrences. For most patients, carefully following product

instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

Nondrug Measures

- Avoid or limit contact with common skin irritants, such as detergents, soaps, and solvents.
- Change clothing and gloves used for cleaning more frequently.
- Wash the affected area gently to remove the skin irritant.

Nonprescription Medications

- Use emollients liberally to restore moisture to skin.
- Use barrier creams if persistent exposure to irritant is anticipated.⁹
 - Apply adequate amounts (e.g., 1g/hand) to entire skin surface that will be exposed. Pay special attention to cutaneous skin folds, cuticles, and skin under nails.
 - Wait 1–3 minutes before exposure.
 - Reapply every 3–4 hours.
- Use colloidal oatmeal baths or soaks to soothe and cleanse areas of the rash and to reduce itching:
 - Sprinkle a 30-g packet or a cupful of fine-ground oatmeal into fast-running bath water and then agitate the water to avoid lumping of the oatmeal.
 - Soak for 15–20 minutes in the oatmeal bath at least twice a day.
 - Pat skin dry rather than wiping it.
 - Oatmeal baths can leave the tub slippery and can clog the drain.
- Store nonprescription medications in a cool, dry place out of children's reach.
- Rash and itching should begin to subside within 5–7 days. If either the rash or the itching worsens, consult your primary care provider.
- Using nonprescription medications longer than 7 days for dermatitis without consulting an appropriate health care provider is not recommended.

Allergic Contact Dermatitis

The goals of self-treatment for allergic contact dermatitis (ACD) are (1) to remove and/or avoid further contact with the offending agent; (2) to treat the inflammation; (3) to relieve itching leading to excessive scratching; (4) to cleanse the skin of debris that accumulates from oozing, crusting, and scaling with release of vesicle contents; and (5) to prevent secondary skin infections. For most patients, carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

Nondrug Measures

- Use the measures outlined in [Table 35–4](#) to prevent poison ivy/oak/sumac dermatitis.
- Take cold or lukewarm, soapless showers to relieve itching.
- When cleansing the affected areas, do not use harsh cleansers or scrub vigorously.
- Use clean white cloths for cool water compresses; apply for 20–30 minutes as often as needed or desired.
- To avoid potential allergic reactions, use hypoallergenic cosmetics and soapless cleansers.

Nonprescription Medications

- If desired, to reduce inflammation and the itching and redness, apply topical hydrocortisone cream *only* as follows:
 - Apply a small amount to affected areas up to 3–4 times a day.
 - Avoid applying the cream around the eyes or on eyelids.
- To avoid infection, do not apply ointments to open lesions.
- Apply aluminum acetate (Burow’s solution) compresses to areas with vesicles, bullae, and/or weeping lesions, as follows:
 - Mix a prepackaged tablet or packet of aluminum acetate with a pint of cool tap water, wet a cloth with the solution, and apply the compress to rash areas.
 - Apply compresses for 20–30 minutes at least 4–6 times a

day or as needed.

– Prepare fresh solution for each application.

- Use colloidal oatmeal baths or soaks to soothe and cleanse areas of the rash and to reduce itching:
 - Sprinkle a 30-g packet or a cup full of fine-ground oatmeal into fast-running bath water, and then agitate the water to avoid lumping of the oatmeal.
 - Soak for 15–20 minutes in the oatmeal bath at least twice a day.
 - Pat skin dry rather than wiping it.
 - Oatmeal baths can leave the tub slippery and can clog the drain.
- Use a sedating oral antihistamine, such as diphenhydramine or doxylamine, for nighttime sedation, and follow the label instructions. These medications can cause drowsiness that may potentially extend to the next morning.
- Store nonprescription medications in a cool, dry place out of children's reach.
- Using nonprescription medications for dermatitis longer than 7 days without consulting an appropriate health care provider is not recommended.

When to Seek Medical Attention

- Contact your primary care provider for the following situations:
 - The rash does not begin to improve in 7 days.
 - The symptoms from the rash worsen.
 - The rash continues to develop for several weeks after initial exposure.
 - Joint swelling or other evidence of systemic involvement emerges.
 - The rash covers large areas of the face or causes swelling of the eyelids.
 - The rash involves the genitals.

Evaluation of Patient Outcomes for Contact Dermatitis

The patient should be encouraged to contact the health care provider for additional advice if the itching has not subsided significantly within 5–7 days. If, at follow-up evaluation, the rash has significantly increased in size, exhibits signs of infection, affects the eyes or genitals, or covers extensive areas of the face, referral to the patient's primary care provider or a dermatologist is warranted. Complete remission of the dermatitis may take up to 3 weeks. However, slow but steady reduction in itching, weeping, and extent and severity of the rash should be evident after 5–7 days of therapy.

Key Points for Contact Dermatitis

- The leading cause of ICD is frequent, unprotected exposure to wet environments that may include irritants such as detergents and cleaning solutions.
- ACD is produced through sensitization to an antigenic substance.
- Many substances are antigenic. Common antigenic substances include fragrances, metals, medications, plants, and chemicals. Urushiol from poison ivy/oak/sumac is one of the most common allergens.
- Patients with recognized sensitivity to specific irritants or allergens including urushiol should take precautions to eliminate exposure by avoiding these agents, limiting exposure time, and wearing protective clothing and equipment.
- Once exposed to an irritant or antigen, the patient should shower with mild soap and water or apply large volumes of cool water to the area immediately after exposure to reduce the risk for development of dermatitis.
- ACD may begin as localized streaks or patches of highly pruritic rash that, with time, may become more numerous or coalesce

into larger plaques on exposed dermal areas. The rash may affect the eyelids or face or, more rarely, less accessible areas such as the axillae or anal region.

- Patients should be referred for further evaluation if there is involvement of the face, genitalia, or anus; signs of infection; considerable edema anywhere on the body (including eyelids); or extensive lesions covering a large portion of the body.
- Treatment of localized, pruritic ACD rash consists of a topical application of hydrocortisone cream or soothing compresses or baths. Zanafel also is recommended to treat localized rash because it may be used for relief any time a rash develops. Weeping vesicles or bullae may be treated with aluminum acetate compresses.
- Irritant and allergic contact dermatitis will resolve in approximately 10–21 days with or without topical therapy. Nonprescription medications primarily relieve symptoms, and improvement should be seen in 5–7 days.

Chapter 36: Diaper Dermatitis and Prickly Heat

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Irritant contact diaper dermatitis (commonly referred to as diaper rash) and prickly heat (also known as miliaria, miliaria rubra, or heat rash) are acute dermatologic conditions that primarily affect infants. In most cases, neither diaper dermatitis nor prickly heat causes serious illness. However, these conditions typically are associated with discomfort, irritation, and itching, which may engender considerable distress, with consequent agitation, irritability, and “fussiness” in infants.

Diaper Dermatitis

Diaper dermatitis is an acute inflammation of the skin occurring in the region of the perineum, buttocks, lower abdomen, and inner thighs. Despite the perception that this condition is limited to infancy, it can and does occur in association with incontinence in any age group.¹ This chapter focuses on infant diaper dermatitis, but the information presented may be generalized to the adult population. (See [Chapter 49](#) for specific information regarding treatment of adult incontinence.) Both irritant contact and allergic contact diaper dermatitis can be the cause of a diaper-area rash.² The primary focus of this chapter is irritant contact diaper dermatitis. Irritant contact diaper dermatitis is referred to simply as *diaper dermatitis* or *diaper rash* throughout. Allergic contact dermatitis is discussed briefly in appropriate contexts.

Diaper dermatitis is the most common dermatologic disorder of infancy, resulting in more than 1 million primary care provider office visits per year.³ In a majority of cases, diaper dermatitis affects infants 2 years of age and younger. Diaper dermatitis can manifest as early as 7 days after birth.⁴ In view of the almost universal practice of diapering, the actual incidence of the condition is likely underreported. Literature has suggested prevalence rates of 7%–50%, with a peak between the ages of 9 and 12 months.^{3,5} However, a majority of children experience diaper dermatitis at least once before they are out of diapers. The steady decline in the number of cases of diaper dermatitis in infants since the 1970s is attributable to the increased use of disposable

diapers. The decline was accelerated in the 1980s and 1990s with improvements in diaper technology and the rise of superabsorbent core materials and breathable diaper coverings.^{6–8}

Pathophysiology of Diaper Dermatitis

Multiple factors have been implicated in the pathogenesis of diaper dermatitis. Occlusion, moisture, microbes, exposure to gastrointestinal tract proteolytic enzymes and bile salts, a shift from the normal acidic skin pH (i.e., 4.0–5.5) to a more alkaline pH, mechanical chafing, and friction all can cause skin compromise, exerting adverse effects in additive or synergistic ways, with diaper dermatitis as the end result.^{3,9–16}

The skin of the infant perineal region is about $\frac{1}{2}$ – $\frac{1}{3}$ the thickness of adult skin. Because the perineal region typically is occluded by a diaper, this area is subjected to prolonged conditions of moisture and wetness, predisposing it to irritation and infection.¹⁷ Frequent urination and defecation, combined with infrequent changing of the diaper, contribute to increased skin moisture. The development of diaper dermatitis is closely related to the exposure to urine and feces along with the occlusion associated with wearing a diaper. The younger the infant, the greater the frequency of elimination. Newborns typically will require a diaper change every 2 hours because of a high wetting frequency, but diaper changes in older infants can be decreased to every 3–4 hours.¹⁸ Skin that remains wet for long periods becomes waterlogged or hyperhydrated, which plugs sweat glands, increases susceptibility to abrasion and frictional harm, and diminishes the barrier function of the stratum corneum in the diaper area. Diminished barrier capabilities, in turn, make the skin more susceptible to irritation, absorption of chemicals, and injury or frank infection by opportunistic microbes.

Urine and fecal bacteria can contribute to skin breakdown. Urea-splitting bacteria from the colon are believed to convert urine components into ammonia. Ammonia raises the pH of the skin, making it more susceptible to damage or infection. The role of this etiologic factor, however, has been lessened by the use of absorbent disposable diapers, which minimize mixing of urine and feces in the diaper area.^{5,19} Mechanical irritation also can lead to epidermal breakdown, allowing other irritants (e.g., fecal bacteria) to harm the skin. Tight-fitting, stiff, or rough diapers and the use of plastic or rubberized covers or pants over cloth diapers can contribute to damage from mechanical

friction and occlusion-induced skin breakdown, respectively.

Medications and foods that affect the motility or microbial flora (e.g., antibiotics) of the gastrointestinal tract, or that hinder autonomic control of urination and defecation, may contribute to diaper dermatitis. Foods high in hexitols, sorbitol, sucrose, and fructose may induce diarrhea and predispose the affected patient to diaper dermatitis. Dairy products can induce diarrhea, especially if the child is lactose-intolerant. (See [Chapter 16](#) for a discussion of diarrhea.) Compared with formula-fed infants, breastfed infants have a decreased incidence of diaper dermatitis.²⁰ The feces of breastfed infants are less copious, less alkaline, and less caustic to the skin. Transitions in the type of food consumed (e.g., from breast milk to solid foods) also can contribute to diaper dermatitis.

Some products (e.g., detergent or soap residues, household cleaning products, lotions, sunscreens, insect repellents), plant materials (e.g., ragweed, thistle), and diaper product ingredients can produce an allergic contact dermatitis that resembles diaper dermatitis.²¹ Many of these agents may not be intended for use in the diaper region, and if present, they may have an unexpected effect on skin under a diaper. Chemicals used to launder and sanitize reusable cloth diapers, if not adequately rinsed, may leave residues that exacerbate diaper dermatitis and skin irritation. Allergic contact dermatitis in the diaper region routinely manifests only in areas of contact with the allergen, often sparing the inguinal skin folds. Allergic contact dermatitis should be considered as a diagnosis when standard care measures do not lead to healing in the diaper area.¹ (See [Chapter 35](#) for discussion of allergic contact dermatitis.)

Clinical Presentation of Diaper Dermatitis

Diaper dermatitis usually manifests as red to bright red (erythematous), sometimes shiny, wet-looking patches and lesions on the skin (see [Color Plates](#), photograph 21). Lesions may appear dusky maroon or purplish on darker skin. Generally, diaper dermatitis involves the skin covered by the diaper, but in severe cases the rash can spread outside the diaper area. If an infant, for example, lies primarily on the abdomen, the rash may appear more anterior to the perineum. In the same manner, if the infant lies primarily on the back, the rash may appear more posterior to the perineum.

A disconcerting feature of diaper dermatitis is that a full-blown rash can

appear in a matter of hours, yet it often can take days to completely resolve. Most likely, the process of skin breakdown is not pronounced or visible initially, but the skin changes quickly undergo transition from unobservable to observable. The entire process from normal to noticeably erythematous skin takes longer than the time between normal diaper changes, so early stages can easily escape detection.

Less commonly, severe diaper dermatitis can progress to maceration, papule formation, the presence of vesicles or bullae, oozing, erosion of the skin, or ulceration. Diaper dermatitis also can predispose affected infants to secondary infections and genital damage. As skin pH changes, it can foster the growth of opportunistic infections that can be bacterial (e.g., streptococci or staphylococci), fungal (e.g., yeasts), or viral (e.g., herpes simplex virus) in etiology. If infection is a concern, visual inspection of the diaper area is beneficial for proper diagnosis. With secondary *Candida* infections, for example, the clinical presentation is distinct from that of uncomplicated diaper dermatitis. The typical *Candida* superinfection manifests as papular or pustular lesions around the margins of the affected area, often with involvement of adjoining skin folds or creases. Untreated or infected diaper dermatitis can progress to skin ulceration, infections of the penis or vulva, and urinary tract infections, all necessitating medical referral.

Diaper dermatitis also can be a manifestation of other diseases and conditions, such as Kawasaki syndrome, granuloma gluteale infantum, cytomegalovirus infection, and nutritional deficiencies. Infants born to immunocompromised mothers (e.g., those with human immunodeficiency virus [HIV] infection or genital herpes) should be considered at increased risk for unusual manifestations of diaper dermatitis or diaper dermatitis-like presentations. Primary infections of the skin can resemble diaper dermatitis and be misdiagnosed. Inguinal swelling, fever, chills, tachycardia, blisters, vesicles, and irregular borders bounded by bumps are indicators of infections that warrant medical referral.^{3,22} Diaper dermatitis can exist concurrently with other skin conditions such as psoriasis and seborrhea¹¹; therefore, these skin conditions may be misdiagnosed as diaper dermatitis.

Treatment of Diaper Dermatitis

Treatment Goals

The goals of diaper dermatitis treatment are (1) to relieve symptoms, (2) to rid the patient of the dermatitis, (3) to prevent secondary infection, and (4) to prevent recurrences.

General Treatment Approach

The general treatment approach for diaper dermatitis is the use of nonpharmacologic measures or a combination of pharmacologic and nonpharmacologic modalities as outlined in [Figure 36–1](#). The components of treatment are identified in the mnemonic ABCDE: *air*, *barrier*, *cleansing*, *diaper*, and *education* ([Table 36–1](#)).¹ The ideal, yet often impractical, preventive practice would be to change the diaper immediately after the infant defecates or urinates. The self-treatment approach often will involve increased caregiver vigilance in keeping the infant dry and use of skin protectants in the diaper area. Management based on the use of self-treatment measures should be limited to diaper dermatitis that is uncomplicated (e.g., absence of comorbid conditions or constitutional symptoms) and mild to moderate (e.g., absence of oozing or blood at lesion sites, or lesions present less than 7 days) in presentation. [Figure 36–1](#) presents a thorough list of characteristics of complicated and severe diaper dermatitis. Medical referral is warranted when one or more of the listed exclusions for self-treatment is present.

TABLE 36–1 ABCDE Mnemonic for Diaper Dermatitis Treatment

A = Air	Allow diaper area skin to air dry frequently; allow diaper-free time.
B = Barrier	Apply barrier skin protectant liberally to diaper area with each diaper change to prevent and treat diaper dermatitis.
C = Cleansing	Gently cleanse the diaper area with a soft cloth and warm water or with a baby wipe when stool is present.
D = Diaper	Change the diaper frequently (every 2 hours) and as soon as it is soiled, if possible. Use absorbent disposable diapers if affordable for the parent/caregiver.
E = Education	Educate parents/caregivers about nonpharmacologic diaper hygiene practices and pharmacotherapy, verifying understanding to ensure adherence.

Source: [Reference 1](#).

Nonpharmacologic Therapy

Nonpharmacologic therapy plays an integral role in the treatment of diaper dermatitis. The goals of nonpharmacologic therapy are (1) to reduce occlusion, (2) to reduce contact time of urine and feces with skin, (3) to reduce mechanical irritation and trauma, (4) to protect the skin from further irritation, (5) to encourage healing, and (6) to prevent secondary infection. Discussing nonpharmacologic measures with parents and other caregivers and ensuring comprehension are critical for adherence and quick resolution.¹

Treatment of uncomplicated diaper dermatitis should be initiated with nonpharmacologic therapy. Increasing the frequency of diaper changes to a minimum of 6 per day is advisable. Although challenging to implement, an effective strategy to prevent diaper dermatitis, known as a *diaper holiday*, is to expose the buttocks to air as long as possible, to limit the duration of contact between skin and wet fabric, in an attempt to reduce friction-induced skin changes.¹⁸

When the perianal area requires cleansing, gentle patting with a chemical-free soft cloth or low-abrasive baby wipe is appropriate. Sensitive-skin baby wipe products are readily available. Used with finesse and gentle technique, baby wipes are as mild on the skin as or milder than washcloths.²³ Few baby wipes still contain alcohol, perfumes, soap, or other ingredients that can cause contact dermatitis or actually burn or sting the infant's skin. Products that list such ingredients on the label should be avoided. Of importance, the unsoiled part of a diaper should never be used to clean or wipe the skin because it may harbor bacteria. An alternative to use of baby wipes is careful rinsing of the skin with warm water followed by gentle nonfriction drying. The infant's diaper area should be allowed to thoroughly air dry before rediapering. Cleansing should be limited to occasions when stool is present to minimize irritation from excessive rubbing.¹

With improving technology, the disposable diaper has become a critical component of nonpharmacologic therapy for diaper dermatitis.^{5,6} Some disposable diapers feature absorptive materials that pull moisture away from direct contact with the skin, to reduce skin hyperhydration and mixing of urine

with feces. Some of these products already contain a protectant (e.g., petrolatum). Disposable diapers with dyes should be avoided because they have been identified as a source of allergic contact dermatitis. Research that compared disposable and cloth diapers indicates that use of disposable diapers decreases the incidence of severe diaper dermatitis.^{5,24-26} When cloth diapers are used, they should be laundered with a mild detergent, with extra rinse cycles if sanitizing agents are used.

Pharmacologic Therapy

The goals of pharmacologic therapy are (1) to protect the skin from further contact with urine and feces, (2) to soothe any discomfort caused by the lesions, (3) to encourage healing, and (4) to prevent secondary infection.

Skin Protectants

Skin protectants serve as physical barriers between the skin and external irritants. Protectants also serve as lubricants in areas in which skin-to-skin or skin-to-diaper friction could aggravate diaper dermatitis or predispose the area to development of diaper dermatitis. Protectants absorb moisture or prevent moisture from coming into direct contact with skin. Protective effects of these products allow the body's normal healing processes to work. Because skin protectants are remarkably safe, their use for both treatment and prevention is acceptable. A skin protectant should be applied with each diaper change to aid in preventing diaper dermatitis.¹⁸

Protectants are the only products considered safe and effective for use in diaper dermatitis without medical referral. The U.S. Food and Drug Administration (FDA) has approved 17 ingredients, all skin protectants, for treatment of infant diaper dermatitis ([Table 36-2](#)).²⁷ Two or more of the approved ingredients are commonly combined in commercial products for treating diaper dermatitis. Of note, some products contain an approved ingredient in combination with other ingredients that are unsafe or of dubious value for treating diaper dermatitis. The other ingredients may be unsuitable or even toxic when applied to skin compromised by diaper dermatitis. Therefore, a general rule is to suggest the simplest possible products that contain FDA-approved ingredients. By law, products that contain antimicrobials, topical analgesics, and antifungals cannot present claims for treatment of diaper dermatitis. Ingredients routinely included in skin

protectant formulations but not approved for treatment of diaper dermatitis are listed in [Table 36–3](#).

TABLE 36–2 FDA-Approved Skin Protectants to Treat Diaper Dermatitis^a	
Agent	Concentration (%)
Allantoin	0.5–2
Aluminum hydroxide ^b	0.15–5
Calamine	1–25
Cocoa butter	50–100
Cod liver oil (in combination)	5.0–13.56
Colloidal oatmeal	≤0.007
Dimethicone	1–30
Glycerin ^b	20–45
Hard fat	50–100
Kaolin	4–20
Lanolin	12.5–50
Mineral oil	50–100
Petrolatum	30–100
Topical cornstarch	10–98
White petrolatum	30–100
Zinc carbonate	0.2–2
Zinc oxide	1–25

^a Owing to safety concerns, products containing sodium bicarbonate and zinc acetate are not appropriate for use in children <2 years of age and have been excluded from this list.

^b Consultation with a primary care provider is suggested before use in infants <6

months of age.

Key: FDA = U.S. Food and Drug Administration.

Source: [Reference 27](#).

TABLE 36–3 Selected Nonmonograph Ingredients in Diaper Dermatitis Products

Aloe	Flower extract	Sweet clover
Beeswax	Honey	Tea tree oil
Calendula	Goldenseal	Vitamin A
Castor oil	Jojoba	Vitamin D
Chamomile	Lavender	Vitamin E
Comfrey	Peruvian balsam	

Of the skin protectants listed in [Table 36–2](#), a select few are commonly incorporated into trade-name skin protectant products. Useful comparative studies of the skin protectants are lacking. Zinc oxide is one of the most commonly used semisolid skin protectants in products that treat diaper dermatitis. A major drawback of many zinc oxide ointment preparations and other hydrophobic diaper dermatitis preparations is the necessity for soap to remove the product from the skin. However, the hydrophobic nature of the preparations is beneficial in forming a protective barrier for the compromised skin. Some zinc oxide preparations are formulated to be more washable and creamlike and are therefore easier to apply and remove. Ease of use, however, must be weighed against ability to adequately protect the skin.

Petrolatum and white petrolatum are commonly used oleaginous ingredients that serve as excellent skin protectants. These products are ubiquitous ointment bases. Petrolatum may be listed as an active or inactive ingredient in skin protectant formulations. Lanolin is a bacteriostatic product obtained from a fatty substance found in wool and also is commonly used alone or in combination with other skin protectants. Although approved for use in diaper

dermatitis, lanolin also is a common contact sensitizer. The risk for sensitization should be considered if lanolin is applied in the diaper area where the skin is inflamed and more vulnerable to contact allergens.

Calamine is a mixture of zinc and ferrous oxides. It has absorptive, antiseptic, and antipruritic properties and is available in numerous dosage forms. Mineral oil coats the skin with a water-impenetrable film that must be washed off with each diaper change to avoid buildup in pores and subsequent folliculitis. Mineral oil often is used in small quantities in skin protectant products. It often is listed as an inactive ingredient in formulations despite FDA approval for use as an active ingredient. Dimethicone is a silicone-based oil that repels water and soothes and counteracts inflammation. It is used in combination with other skin protectants such as zinc oxide.

Topical cornstarch and talc are used as loose powders. They provide benefit by reducing moisture and friction.¹ Topical cornstarch is an absorbent material, whereas talc functions as a lubricant. Both products carry warnings against inhalation of the powder because of an associated risk of severe respiratory disease. The warning states: “Keep powder away from child’s face to avoid inhalation, which can cause breathing problems.”²⁷ Some health care providers suggest pouring the powder into the hands away from the infant and gently rubbing it onto the perineal area; however, because of the inhalation risk, these products should be avoided.¹ Talc specifically should not be applied to broken or oozing skin; it can cake on the edges of wounds, potentially precipitating infection or retarding healing. In addition, two recent meta-analyses found an association between perineal talc use and ovarian cancer.^{28,29} Although the results of these studies are for women and not infants, it may be advisable to avoid use of talc altogether.

Although it has not been studied for safety and efficacy, an aluminum hydroxide–magnesium hydroxide oral antacid suspension has become a popular topical agent for treatment of diaper dermatitis when mixed with Aquaphor.¹ Burow’s solution (aluminum acetate in water) has been compounded with petrolatum and zinc oxide to form 1-2-3 Paste, which also has been used for irritant contact dermatitis in the diaper area despite a lack of supporting clinical evidence.¹ **Table 36–4** lists selected widely available trade-name products and their active ingredients.

TABLE 36–4 Selected Nonprescription Products for Diaper Dermatitis

Trade Name	Primary Ingredient(s) (With Selected Additional Ingredients)
A + D Original Ointment	Petrolatum 53.4%; lanolin 15.5% (cod liver oil; mineral oil; beeswax ^a)
A + D Zinc Oxide Cream	Zinc oxide 10%; dimethicone 1% (aloe vera ^a ; coconut oil ^a ; cod liver oil; mineral oil; beeswax ^a)
Aquaphor Baby Healing Ointment	Petrolatum 41% (lanolin; mineral oil)
Baby Anti Monkey Butt Diaper Rash Powder	Calamine powder 8% (cornstarch)
Balmex Diaper Rash Cream	Zinc oxide 11.3% (beeswax ^a ; dimethicone; mineral oil; soybean oil ^a ; evening primrose ^a ; olive leaf extract ^a)
Boudreaux's Original Butt Paste	Zinc oxide 16% (castor oil ^a ; mineral oil; paraffin ^a ; balsam ^a ; petrolatum)
Burt's Bees Baby Bee Natural Diaper Rash Ointment	Zinc oxide 40% (sweet almond oil ^a ; beeswax ^a ; lanolin; castor oil ^a ; jojoba oil ^a ; shea butter ^a ; olive oil ^a ; chamomile ^a ; lavender oil ^a ; calendula ^a ; rosemary ^a ; soybean oil ^a ; canola oil ^a)
CeraVe Baby Healing Ointment	Petrolatum 46.5% (mineral oil, dimethicone)
Desitin Maximum Strength Original Paste	Zinc oxide 40% (cod liver oil; lanolin; petrolatum; talc ^a)
Desitin Multi-Purpose Healing Ointment	White petrolatum 71.3% (mineral oil; paraffin ^a ; cocoa butter)
Desitin Daily Defense Cream	Zinc oxide 13% (mineral oil; petrolatum; beeswax ^a ; dimethicone; aloe ^a ; glycerin)
Flanders Buttocks Ointment	White petrolatum 66.2%; zinc oxide 13.4% (beeswax ^a ; castor oil ^a ; mineral oil; Peruvian balsam ^a)
Triple Paste Medicated Ointment	Zinc oxide 12.8% (cornstarch; lanolin; white petrolatum; beeswax ^a)

^a Nonmonograph ingredients.

Skin protectant dosing and application are straightforward. The protectant is applied liberally to the skin in the diaper area. Any remaining protectant from the previous diaper change should not be removed, to minimize additional irritation that may result from the rubbing. Special attention is needed to ensure complete coverage of erythematous areas with the protectant if diaper dermatitis is already present. Overapplication (overdosage) of approved skin protectants is not a concern. Underapplication, however, can reduce the protective effect of the product. The protectant should be reapplied as needed and with every diaper change. Research suggests that applying a skin protectant regularly with each diaper change is an important element of prevention of diaper dermatitis.¹³ Skin protectants do not interact with other agents; however, the use of ointment preparations will preclude retention of other topically applied products. With diaper dermatitis that does not necessitate medical referral, dramatic improvement commonly is seen within 24 hours of initiation of pharmacologic and nonpharmacologic treatment.

Contraindicated Agents

Topical nonprescription antibiotic and antifungal agents are not appropriate for use in the self-treatment approach to diaper dermatitis. If an infection is suspected, medical referral is advised. Topical analgesics also are not recommended because they can alter sensory perception in a population in which the ability to communicate such changes often has yet to mature. These agents also may excoriate macerated skin, cause pain, and retard healing, thereby further complicating diaper dermatitis.

Hydrocortisone is indicated for minor skin irritation but should not be used in diaper dermatitis without supervision by an appropriate health care provider. Hydrocortisone can increase the risk of secondary infection via immune response suppression. Additionally, the diaper area constitutes a significant proportion of the infant's body surface area. Hydrocortisone absorption into the skin is enhanced under occlusive conditions. When this agent is applied to macerated skin or a large surface area, its absorption may lead to serum levels that interfere with the infant's pituitary–adrenal axis. Nonprescription

hydrocortisone is labeled to be avoided in patients younger than 2 years. (See [Chapter 35](#) for additional information on the use of hydrocortisone.)

Product Selection Guidelines

Although no particular product among those approved for diaper dermatitis possesses evidence-based advantages, personal preferences for certain product characteristics will likely determine which product caregivers use to treat diaper dermatitis. As previously mentioned, some commonly used products contain nonapproved (i.e., nonmonograph) ingredients. These products may be used for formulation purposes, or they may be unregulated nutraceuticals listed as inactive or active ingredients. Unapproved ingredients also could be included in preparations to support marketing claims. For example, camphor may be present to provide a “medicated” fragrance; aloe may be present to appeal to the public perception that aloe is a wound-healing agent; or vitamins may be present to convey “natural” characteristics. To make the claim to treat diaper dermatitis, the product, however, must meet FDA-published guidelines for active ingredients. Although diaper dermatitis is a condition primarily of infants and older adults, no additional concerns have emerged in relation to product selection in these age groups.

Complementary Therapies

Complementary therapies are not recommended for use in newborns and infants because of insufficient evidence regarding their safety and effectiveness in these populations. Rates of systemic absorption are unknown. Although some of these agents have been used without incident in adults, no credible data on their safety or efficacy in infants are available. Recently, honey has received attention as a treatment option for diaper dermatitis; it has been used for several years in wound care. Manuka honey in particular has been found to have hygroscopic, fungicidal, and antibacterial properties and helps to regulate the mildly acidic pH of the skin. Initial studies have shown honey, beeswax, and olive oil to be effective in management of diaper dermatitis.³⁰ Although these agents should not be recommended at this time, with more robust studies, they may become acceptable therapeutics in the future.

Assessment of Diaper Dermatitis: A Case-Based Approach

When a caregiver or patient seeks information about management for suspected diaper dermatitis, the health care provider should evaluate the presentation of the diaper-area rash itself and assess for the presence of any factors conducive to exacerbation of diaper dermatitis. Under appropriate conditions, visual inspection of the affected area is indicated. In settings that preclude such inspection, open-ended questioning techniques will yield an adequate description of the dermatitis. Case 36–1 illustrates assessment of a patient with diaper dermatitis. If the problem is deemed to be uncomplicated diaper dermatitis amenable to a self-care approach, appropriate nonpharmacologic and pharmacologic modalities should be recommended. Nonpharmacologic management should begin with establishing the type of diaper being used and the frequency of diaper changes. On this basis, the provider can consider whether increasing the frequency of diaper changes and other nonpharmacologic measures are likely to be sufficient to heal the diaper dermatitis or whether pharmacologic treatment is warranted. In view of the minimal risk associated with use of pharmacologic products approved for treatment, various options are available for recommendation to the patient or caregiver ([Table 36–2](#)).

Algorithm: Diaper Dermatitis

FIGURE 36–1 Self-care for diaper dermatitis. Key: HIV = Human immunodeficiency virus; OTC = over-the-counter.

Case 36–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	

Relevant Evaluation Criteria	Scenario/Model Outcome
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	A parent seeks advice on treatment for his infant daughter's pronounced red rash on the diaper area. He reports that she woke up from a nap a little fussy, and he noticed the rash while changing her diaper. He is "in shock," he states, because the rash seemed to appear "out of nowhere." He describes the affected skin as bright red and shiny and sensitive to any touch. His daughter cried when he was cleaning her bottom with a baby wipe.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Similar rashes have occurred before, but the baby's father cannot remember which cream he used. Previous rashes have resolved without any need to see the pediatrician.
c. Description of the patient's/caregiver's efforts to relieve the symptoms	The father has not tried anything so far. In general, he uses disposable diapers and sensitive-skin baby wipes.
d. Patient's identity	Aurora William
e. Patient's age, gender, height, and weight	6 months, female, 25 in., 16 lb
f. Patient's occupation	n/a
g. Patient's dietary habits	Aurora is formula-fed 6 times daily; her father is beginning to introduce baby cereal and prepared baby food into her diet.
h. Patient's sleep habits	Normal for age
i. Concurrent medical conditions,	None

Relevant Evaluation Criteria	Scenario/Model Outcome
prescription and nonprescription medications, and dietary supplements	
j. Allergies	NKA
k. History of other adverse reactions to medications	None noted
l. Other (describe) -----	n/a
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Findings are consistent with mild to moderate diaper dermatitis. The description of the rash, along with the quick onset and the child's irritability and sensitivity, supports this diagnosis.
3. Identify exclusions for self-treatment (Figure 36-1).	None noted
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Recommend self-care with drug, nondrug, and/or complementary therapies. (2) Refer the patient to her pediatrician or other primary care provider for treatment. (3) Recommend a self-care approach until an appropriate health care provider can be consulted. (4) Take no action.
Plan	

Relevant Evaluation Criteria	Scenario/Model Outcome
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	The best option would be to use both nonpharmacologic measures and nonprescription products to treat the rash. Specifically recommend increased diaper changes and allowing the area to air dry between diaper changes. Also recommend liberal application of skin protectant (see Table 36–4 for a listing of available products) with every diaper change as needed. Use of the product may be continued after the rash heals, to prevent future diaper rash.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"A skin protectant will help protect Aurora's skin from further irritation and will allow the diaper rash to heal. Changing her diaper more often and allowing the skin to air dry will quicken healing time and reduce the likelihood of the rash coming back. You also should use plain warm water or sensitive-skin baby wipes to clean the area before air drying."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Based on the appearance of Aurora's diaper rash, you should be able to use nonprescription products for treatment. She currently does not need to see her pediatrician, but be sure to contact an appropriate health care provider if no improvement is seen within 7 days, if the skin under her diaper looks worse, or if she shows any other symptoms or skin changes not limited to the diaper area."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
a. Appropriate dose and frequency of administration	"Apply Desitin Daily Defense Cream liberally to the affected area with every diaper change and as needed."
b. Maximum number of days the therapy	"Skin protectants can be applied to both treat and prevent diaper rash. There is no maximum length of therapy for this medication."

Relevant Evaluation Criteria	Scenario/Model Outcome
should be employed	However, if the rash and sensitivity do not subside within 7 days, seek medical attention.”
c. Product administration procedures	“Wash your hands and clean the diaper region with a sensitive-skin baby wipe or plain warm water. Allow the area to thoroughly air dry. Then apply the cream to the diaper region liberally. Change diapers at least 6 times a day, every 3–4 hours at a minimum.”
d. Expected time to onset of relief	“You should see noticeable improvement in the affected skin within 24 hours.”
e. Degree of relief that can be reasonably expected	“The rashy area will become less tender with continued application. The skin should return to normal within 7 days—more quickly if diapering technique is adjusted.”
f. Most common adverse effects	“There are no common adverse effects reported with this product.”
g. Adverse effects that warrant medical intervention should they occur	n/a
h. Patient/caregiver options in the event that condition worsens or persists	See the box “Patient Education for Diaper Dermatitis” and Figure 36–1 .
i. Product storage requirements	“Store this product out of reach of children and away from heat and moisture.”
j. Specific nondrug measures	See the box “Patient Education for Diaper Dermatitis.”
Solicit follow-up questions from the patient or caregiver.	“What are the differences between the various diaper rash products?”
Answer the patient’s or caregiver’s questions.	“Ointments, pastes, and creams usually are preferred over powders, which can be dangerous if inhaled. Almost all of the agents provide similar benefit and lack any major adverse effects. Children may be sensitive to products containing lanolin, especially if they suffer from other allergies. Products containing mineral oil must be washed off

Relevant Evaluation Criteria	Scenario/Model Outcome
	with each diaper change, to avoid occurrence of folliculitis. Zinc oxide and other greasy products require soap for removal from the skin. It probably is best to avoid products containing any extra 'natural' ingredients, which usually lack evidence of benefit."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Ask Mr. William to call you in 2 days to discuss how Aurora's rash is resolving with the suggested treatment plan.

Key: n/a = Not applicable; NKA = no known allergies.

Patient Education for Diaper Dermatitis

The goals of diaper dermatitis treatment are (1) to relieve the symptoms, (2) to rid the patient of the dermatitis, (3) to prevent secondary infection, and (4) to prevent recurrences. For most patients, carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

Nondrug Measures

- Use the mnemonic ABCDE (*air, barrier, cleansing, diaper, education*) in managing diaper dermatitis.
- Change diapers frequently, at least 6 times a day, to limit exposure of the infant's skin to moisture and feces.
- Do not use rubber or plastic pants over cloth diapers. Tightly covering the skin encourages skin breakdown.
- When stool is present, use plain water to clean the diaper area. Gently dry area or allow it to air dry.

- Do not wipe the infant with any part of the diaper. Even areas that appear clean may be contaminated with fecal bacteria.
- Avoid commercial baby wipes that contain alcohol, perfumes, and soap, which may burn or sting the skin.
- If feasible, allow the infant to go without a diaper, even for very short periods, to promote drying of the rash.

Nonprescription Medications

- To treat diaper dermatitis, use a product containing one or more of the skin protectants listed in [Table 36–2](#). The product can be used even after the rash clears to prevent recurrences.
- Do not use products that contain ingredients listed in [Table 36–2](#) if they are combined with benzocaine or an antibacterial such as benzethonium chloride. Benzocaine can cause an allergic reaction; antibacterials are not suitable for use with diaper dermatitis.
- Do not use hydrocortisone.
- Do not use topical (external) analgesics such as phenol, menthol, methyl salicylate, or capsaicin to treat diaper rash. These medications are inappropriate for use on infant skin and may cause harm.
- Powders for children or infants should ideally be avoided; if used, they should be gently poured into the caregiver’s hands away from the infant’s face and then rubbed onto the skin, using a sufficient amount to cover the affected area. Do not vigorously shake powders near the infant. Avoid infant or self-inhalation of powders.
- Apply cream or ointment liberally to cover the affected area.
- If mineral oil has been applied, wash it off at every diaper change to avoid clogging skin pores.
- Throw away products that are discolored or whose expiration dates have passed. (The health care provider should point out expiration dates on the products.)

When to Seek Medical Attention

- Consult a primary care provider if any of the exclusions in [Figure 36–1](#) apply.

Patient Counseling for Diaper Dermatitis

Patient and caregiver counseling should begin with education on proper cleaning of the diaper area. Recommendations for self-care management also should emphasize the need to avoid occlusion of the area, when feasible, and to avoid prolonged contact of urine or feces with the infant's skin. The health care provider should explain the proper methods of applying nonprescription skin protectants and should identify signs and symptoms indicating that the dermatitis has worsened and warrants medical attention. The box "Patient Education for Diaper Dermatitis" lists specific information to provide in patient and caregiver counseling.

Evaluation of Patient Outcomes for Diaper Dermatitis

Treatment for diaper dermatitis should be of relatively short duration. If 7 days of treatment have elapsed and the condition is not showing signs of healing, medical referral is warranted. At the conclusion of therapy, the skin should return to its pre-diaper dermatitis condition. If diaper dermatitis occurs routinely or is severe, prophylactic use of skin protectants is suggested; the safety of the various preparations presented in [Table 36–2](#) is well established.

Prickly Heat

Prickly heat, also known as heat rash, is a transient inflammation of the skin that appears as a very fine, pinpoint, and usually red raised rash. It can appear on any part of the body that has sweat glands (e.g., groin, chest, axillae). This condition may occur in patients of any age with active sweat glands.³¹ The highest incidence is during the first month of life and in up to 30% of adults living in hot and humid conditions.³¹ This condition is likely underreported because it is less troublesome than diaper dermatitis and generally clears up rapidly. Prickly heat often manifests in hot working conditions and with activities associated with sweating (e.g., manual labor, exercise, athletics).^{32,33}

Pathophysiology of Prickly Heat

Prickly heat results from partially clogged sweat glands. (See [Chapter 38](#) for a review of the anatomy of the sweat gland.) The trapped sweat causes dilation and rupture of epidermal sweat pores, resulting in acute inflammation of the dermis that may manifest as stinging, burning, or itching.

Prickly heat can arise from normal skin with little or no physiologic prodrome. The condition is most often associated with very hot, humid weather or during illnesses that cause significant or profuse sweating. It is commonly associated with the inability of the skin to “breathe” because of excessively tight, flame-resistant, or occlusive clothing such as leather, polyester, athletic clothing materials (e.g., neoprene), or athletic protective or safety garments and devices.³⁴ Chemicals added during the laundering process also can be a cause of prickly heat.³⁵

Clinical Presentation of Prickly Heat

The hallmark presentation of prickly heat is pinpoint-sized lesions that are raised and red or maroon, forming erythematous papules (see [Color Plates](#), photograph 22). The lesions may appear in small numbers clustered together or spread over the occluded area on a pink to red field (miliaria rubra). Common sites for prickly heat dermatitis include the axillae, chest, upper back, back of the neck, abdomen, and inguinal area. The lesions often trace the pattern of the occlusion and, in uncomplicated cases, do not extend beyond the occluded area. If resolution does not occur within a reasonable period (approximately 3–10 days) after correction of etiologic factors, the condition can evolve into the same kinds of complications seen in diaper dermatitis (e.g., infection, pustule formation, generalized dermatitis). Complications, however, are extremely rare.

Treatment of Prickly Heat

Treatment Goals

The primary goal of treatment in prickly heat is removal of the causative agent or agents. Lesions associated with prickly heat usually resolve without pharmacologic treatment if the cause is removed. A secondary goal in the

treatment of prickly heat is alleviation of symptoms associated with the condition.

General Treatment Approach

The nonpharmacologic treatment goals for prickly heat are (1) to eliminate occlusion of skin, (2) to protect skin from further irritation, (3) to promote healing of skin, and (4) to prevent secondary infection.

Pharmacologic therapy for prickly heat has the same goals, with approved products chosen to help keep skin dry, soothe any discomfort caused by lesion(s), promote healing, and prevent secondary infection.

The algorithm in [Figure 36–2](#) outlines self-treatment for prickly heat.

Nonpharmacologic Therapy

Nondrug therapy for prickly heat includes measures to decrease sweating and to increase air flow to the affected area. If the sweating is caused by a fever, use of systemic antipyretics may be appropriate, unless contraindicated. Wearing loose, light-colored, and lightweight clothing is palliative in prickly heat, allowing airflow to the skin. Cooling baths and use of air conditioning also will be helpful in symptom management. To that end, all excess clothing should be removed. Patients must be warned not to apply oleaginous substances to prickly heat lesions because these substances plug pores that need to be patent.

Pharmacologic Therapy

Pharmacologic therapy with nonprescription products for relief of prickly heat should be limited to mild to moderate, uncomplicated cases. Affected areas should not be occluded during therapy. Overall, this disorder can be ameliorated in less time and with less total drug exposure than are required for diaper dermatitis.

Emollients, Skin Protectants, and Antipruritics

A drug product that relieves burning and itching and does not block exposure of skin to air should be used to treat the symptoms of prickly heat. Options include water-washable antipruritic products, as well as bland emollients and

protectants that soothe the skin and maintain skin moisture and texture. Colloidal oatmeal bath products and lotions also are useful because of their antipruritic and soothing properties. Powders should be used only prophylactically to absorb moisture and keep skin dry. (See [Table 36–5](#) for selected trade-name products and [Chapter 33](#) for a discussion of skin emollients.)

TABLE 36–5 Selected Nonprescription Products for Prickly Heat

Trade Name	Primary Ingredient(s) (With Selected Additional Ingredients)
Aveeno Daily Moisturizing Lotion	Dimethicone 1.2% (glycerin; oat kernel flour)
Extra Strength Benadryl Itch Stopping Cream	Diphenhydramine HCl 2%; zinc acetate 0.1%
Cortizone-10 Maximum Strength Anti-Itch Cream	Hydrocortisone 1% (aloe; beeswax; glycerin; mineral oil; petrolatum)
Eucerin Calming Itch Relief Treatment	Menthol 0.1% (glycerin; colloidal oatmeal; dimethicone; evening primrose oil; castor oil)
Lubriderm Daily Moisture Lotion	Water; mineral oil; glycerin; dimethicone

Other Pharmacologic Agents

As with diaper dermatitis, hydrocortisone is contraindicated in infants. In adults, hydrocortisone may be useful if the body surface area involved is 10% or less. (See [Figure 41–3](#) for information on calculating body surface area.) Because prickly heat rapidly clears without drug therapy, hydrocortisone should be used only when relief of itching is required. Topical antihistamines and local anesthetics (see [Chapter 37](#)) carry the risk of sensitization, but they can be used as antipruritic agents. Patients who have a fever, in whom the associated sweating may be causing prickly heat, can use standard systemic analgesics to manage the fever (see [Chapter 6](#)).

Product Selection Guidelines

In treating prickly heat, the skin needs to dry and dissipate moisture. Therefore, only water-washable, cream-based products should be used. For moisture absorption and prevention of wetness, powders are reasonable;

however, prolonged use or overuse can lead to clogged pores, precipitating prickly heat. For use on the chest or neck, cornstarch or talc powder should be placed in the hand and applied manually to the skin with light friction to avoid inhalation, which can cause severe respiratory disease. Any product that has a potentially toxic ingredient (e.g., phenols, boric acid) if absorbed through thin, compromised skin should not be recommended for infants. Bathing children and infants who have prickly heat in colloidal oatmeal or lukewarm water may be recommended as a first option.

Assessment of Prickly Heat: A Case-Based Approach

Patient assessment for prickly heat involves identifying the site(s) of the lesions and potential causes. If the patient is an infant, the health care provider should gather information regarding potential environmental characteristics (e.g., sleeping conditions, presence/absence of air conditioning) that could be exacerbating the condition.

Case 36–2 provides an example of assessment of a patient with prickly heat.

Algorithm: Prickly Heat

FIGURE 36–2 Self-care for prickly heat. Key: OTC = over-the-counter; PCP = primary care provider.

Case 36–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	

Relevant Evaluation Criteria	Scenario/Model Outcome
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient seeks advice from the pharmacist regarding treatment for “red bumps that look like tiny dots” on his chest and back. He has had the rash for 2 days. He states that the rash is itchy but not painful.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient’s symptom(s)	Patient seems to get this rash every summer. He is training for a marathon and notices the rash when he wears athletic workout apparel.
c. Description of the patient’s efforts to relieve the symptoms	Patient tries to prevent rash through good personal hygiene techniques (e.g., taking showers more frequently) and applying a thick cream to problem areas to keep them moist; however, these measures do not always prevent the rash.
d. Patient’s identity	Tho Nguyen
e. Patient’s age, gender, height, and weight	28 years, male, 5 ft 10 in., 170 lb
f. Patient’s occupation	Accountant and marathon runner
g. Patient’s dietary habits	Normal diet; social drinker
h. Patient’s sleep habits	Averages 7 hours of sleep nightly.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	None
j. Allergies	Allergy to penicillin (hives)
k. History of other adverse reactions to medications	None
l. Other (describe) _____	n/a
Assess	
2. Differentiate patient’s signs/symptoms, and correctly identify the patient’s primary	Prickly heat secondary to sweating, exercise, heat, and occlusion from athletic wear and equipment

Relevant Evaluation Criteria	Scenario/Model Outcome
problem(s).	
3. Identify exclusions for self-treatment (Figure 36-1).	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Recommend self-care with drug, nondrug, and/or complementary therapies. (2) Refer the patient to an appropriate health care provider for treatment. (3) Recommend self-care until an appropriate health care provider can be consulted. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Patient education about the cause of prickly heat is important in prevention of future occurrences. Colloidal oatmeal lotions should provide relief from itching and also provide soothing benefits. Powders may be used prophylactically to absorb moisture. Cooling baths and air conditioning also are recommended.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Discontinue the thick cream because it can block pores, worsening your prickly heat. Topical hydrocortisone will help with the itching, but do not apply it more than 3-4 times a day and to more than 10% of your body."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Prickly heat often heals with time once the cause is removed and can be effectively managed with nonprescription products and improved hygiene practices. Keeping the area dry and minimizing clogged pores are key measures. If relief of itching is needed, hydrocortisone is preferred, because topical antihistamines and local anesthetics carry the risk of sensitization."
Implement	
8. When recommending self-	

Relevant Evaluation Criteria	Scenario/Model Outcome
care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
a. Appropriate dose and frequency of administration	“Cortizone 10 Maximum Strength: apply to affected area(s) not more than 3–4 times daily as needed. Johnson’s Baby Powder: apply 1 time daily after showering. Be careful not to inhale powder.”
b. Maximum number of days the therapy should be employed	“Use of nonprescription protectants and self-treatment measures for prickly heat is limited to 7 days.”
c. Product administration procedures	See the box “Patient Education for Prickly Heat.”
d. Expected time to onset of relief	“The itching and rash should start to subside within 24 hours or less if nonpharmacologic measures are employed as directed.”
e. Degree of relief that can be reasonably expected	“Skin should return to normal within 7–10 days; protectants may not provide sufficient itch relief. Prickly heat is likely to return if nonpharmacologic strategies are not implemented.”
f. Most common adverse effects	Powders used in excess may clog pores, exacerbating the condition.
g. Adverse effects that warrant medical intervention should they occur	Respiratory inhalation of powders
h. Patient options in the event that condition worsens or persists	See “Exclusions for Self-Treatment” in Figure 36-1 .
i. Product storage requirements	“Store this product out of reach of children and away from heat and moisture.”
j. Specific nondrug measures	See “Nondrug Measures” in the box “Patient Education for Prickly Heat.”

Relevant Evaluation Criteria	Scenario/Model Outcome
Solicit follow-up questions from the patient or caregiver.	"Are there specific athletic clothing items that make this better or worse?"
Answer the patient's or caregiver's questions.	"Any type of tight or occlusive clothing will worsen or make prickly heat more likely. Neoprene materials in athletic clothing have been found to make prickly heat more likely. Wearing loose athletic clothing and removal of clothing immediately after working out and then showering will minimize your risk."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Ask Mr. Nguyen to call you in 3 days to update you on his response to your treatment plan.

Patient Counseling for Prickly Heat

The health care provider should emphasize that prickly heat usually is easily treated by removing factors that clog skin pores, while also explaining appropriate nonpharmacologic and pharmacologic measures for promoting healing or alleviating symptoms. An important point to include in patient education is that excessive use of skin protectants can exacerbate the disorder. The box "Patient Education for Prickly Heat" lists specific information to provide in patient counseling.

Evaluation of Patient Outcomes for Prickly Heat

Treatment for prickly heat should be of relatively short duration. Considerable improvement is commonly noted in as little as 24 hours after initiation of nonpharmacologic and pharmacologic therapy. If the condition is not completely resolved or has worsened after 7 days of treatment, referral for further medical evaluation is indicated. Monitoring of treatment success

involves simple observation of lesions. At the end of therapy, the affected skin should have returned to its precondition state.

Patient Education for Prickly Heat

The goals of self-treatment are (1) to relieve the discomfort of prickly heat and (2) to eliminate its cause. For most patients, following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

Nondrug Measures

- To prevent clogging skin pores, avoid excessive sweating by resting, cooling off, or going to a cool environment.
- Wear loose, light-colored, breathable, and lightweight clothing to allow airflow to the skin.
- Shower, bathe, or change clothes immediately after heavy sweating, and wear loose-fitting clothes when such activity is anticipated. Remember to drink plenty of fluids, and allow the body to cool down after any strenuous activity.

Nonprescription Medications

- Unless a health care provider advises otherwise, use systemic analgesics, such as acetaminophen or ibuprofen, to reduce a fever and the sweating it can cause. (See [Chapter 6](#) for dosing information.)
- Do not apply oily substances to prickly heat lesions because they clog skin pores.
- Use powdered skin protectants to absorb moisture and help prevent wetness ([Table 36–4](#)). Place cornstarch or talc powder in the hand, and apply to the skin with light friction. Note that prolonged use or overuse of powders can lead to clogged pores, which can precipitate prickly heat.
- Do not use hydrocortisone in infants. However, it may be used to relieve itching in adult cases of prickly heat if no more than 10% of

the body surface area is involved.

- Water-washable emollients applied in a thin film twice a day can help the skin return to normal. (See [Chapter 33](#).)
- If redness, burning, itching, peeling, or swelling develops after a product is applied, rinse any remaining product off the skin and avoid further use.
- To soothe discomfort in adults or infants, wash the affected skin with bland soap or soak the area in a colloidal oatmeal solution.
- The condition should respond with observable improvement in 24 hours.

When to Seek Medical Attention

- If the condition persists after 7 days of treatment, consult a primary care provider.

Key Points for Diaper Dermatitis and Prickly Heat

Diaper Dermatitis

- Diaper dermatitis is exacerbated by moisture and occlusion.
- Increasing the frequency of diaper changes (i.e., decreasing contact time between skin and urine/feces) plays a major role in the nonpharmacologic management of diaper dermatitis.
- Pharmacologic therapy should be limited to use of products containing FDA-approved ingredients indicated for the treatment of diaper dermatitis ([Table 36–2](#)); exotic additives and complementary therapies should be avoided.
- Apply hydrophobic skin protectants liberally to diaper dermatitis areas; over application should not be a concern.

- Do not use hydrocortisone in the self-treatment approach to diaper dermatitis.
- A majority of diaper dermatitis cases will resolve when occlusion and wetness are adequately suppressed.
- With diaper dermatitis that persists after 7 days of treatment, the patient should be referred for further medical evaluation.

Prickly Heat

- Prickly heat is exacerbated by heat, humidity, and occlusion.
- Generally, prickly heat will resolve when occlusion and wetness are adequately suppressed.
- Pharmacologic treatment of prickly heat should be targeted at providing relief from itching or burning.
- Products containing emollients or anti-itch ingredients in water-washable dosage forms are favored in the treatment of prickly heat. Powders may be used to help dry the skin, albeit judiciously to avoid clogged pores, and careful application technique is essential to prevent inhalation.
- With prickly heat that persists after 7 days of treatment, the patient should be referred for further medical evaluation.

Chapter 37: Insect Stings and Bites and Pediculosis

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Insect bites and stings are common, and anyone who spends time outdoors is at risk. These injuries usually cause only a local reaction, but they can produce a mild allergic reaction or life-threatening anaphylaxis in patients who are sensitive to compounds in the insect's saliva or venom. Approximately 0.5%–3% of the population may show signs of systemic allergic reactions to insect stings, and simultaneous multiple insect stings of 500 or more may cause death from toxicity.¹ In the United States, more people die of insect stings than of bites from all poisonous animals combined.² The exact number of people who experience systemic allergic reactions to insect bites is unknown.

Despite the potentially fatal consequences, encounters with biting and stinging insects are typically brief. Pediculosis (lice infestation) and scabies, however, are parasitic infections, and the arachnids remain on the host until eradicated. Approximately 10–12 million people in the United States are affected by pediculosis each year, most of them children ages 3–12 years.³

This chapter covers the stings of insects only but discusses the bites of both insects and arachnids (e.g., ticks, mites, spiders, lice). The term *insect* is used to cover general statements about these invertebrates.

Insect Bites

Pathophysiology and Clinical Presentation of Insect Bites

Bites from insects (e.g., mosquitoes, fleas, bedbugs) and arachnids (e.g., ticks, mites, spiders, lice) are nonvenomous. Each insect has distinctive biting organs and salivary secretions that contribute to the characteristic signs and symptoms for each type of bite.

Mosquitoes

Mosquitoes are found in abundance worldwide, particularly in humid, warm climates. After landing on the skin, mosquitoes inject an anticoagulant saliva into the victim, which causes the characteristic welt and itching. These bites may expand into larger blisters or urticarial reactions with systemic symptoms of fever and joint swelling in some patients. Although rare, anaphylaxis may occur.⁴

Mosquitoes serve as vectors for spreading serious systemic infections including malaria and West Nile, Chikungunya, and Zika viruses, with West Nile virus being the most common.⁵ Although most patients infected with West Nile virus do not experience symptoms, about 20% of infected patients experience influenza-like symptoms with fever, fatigue, and possible joint pain. Few patients experience severe symptoms, and the illnesses are rarely fatal.⁶

Fleas

Fleas are tiny bloodsucking insects that can be found worldwide but breed best in a humid climate. Humans often are bitten after moving into a vacant flea-infested habitat or when living with infested pets. Flea bites usually are multiple and grouped and, in humans, primarily occur on the legs and ankles. Each lesion is characterized by an erythematous region around the puncture and intense itching. In addition to being annoying, fleas can transmit diseases such as bubonic plague and endemic typhus.⁷

Sarcoptes scabiei

Scabies is a contagious parasitic skin infection caused by *Sarcoptes scabiei*, a very small and rarely seen arachnid mite.⁸ The mites burrow up to 0.4 in. (1 cm) into the stratum corneum, and the females then deposit eggs in their “tunnels.” Common infestation sites are interdigital spaces of the fingers, flexor surfaces of the wrists, external male genitalia, buttocks, and anterior axillary folds (see [Color Plates](#), photograph 23). Scabies infection is characterized by inflammation with a papular rash and intense itching, although symptoms may not appear for 4–6 weeks. Mites are transmitted from an infected individual to others through physical contact. A scabies infection requires treatment with prescription drugs.

Bedbugs

Bedbugs usually hide and deposit their eggs in crevices of walls, floors, picture frames, bedding, folds of linens, corners of suitcases, and furniture during the day; they bite their victims at night. The increased mobility of society worldwide has heightened concern for an increased incidence of bedbug infestations in the United States in places frequented by travelers, such as hotels.⁹ In addition, bedbugs have developed resistance to commonly used pesticides. Bedbug bites typically appear along exposed areas of skin, such as the head, neck, and arms.¹⁰ Bites occur in clusters and may appear in a straight line. It may take several days for a bite mark to appear. The reaction to a bedbug bite can range from irritation at the site to a small dermal hemorrhage, depending on the sensitivity of the individual; however, most of these bites involve intense itching.

Ticks

Ticks feed on the blood of humans and animals. During feeding, the tick's mouthparts are introduced into the skin, enabling it to hold firmly (see [Color Plates](#), photograph 24). If the tick is removed, but the mouthparts are left behind, intense itching and nodules requiring surgical excision may develop. If left attached, the tick becomes fully engorged with blood and remains for up to 10 days before dropping off. Ticks should be removed intact using fine tweezers within 36 hours of attachment. Tick removal by heating methods, such as a match or hot nail, or by painting substances onto the tick, such as nail polish or petrolatum, is not recommended. These methods can irritate the tick, causing it to secrete more saliva or even regurgitate gut contents, thereby increasing the likelihood of transmission of a tick-borne illness. After removal of the tick, the affected area should be cleaned with rubbing alcohol or washed with soap and water.¹¹

The local reaction to tick bites consists of itching papules that disappear within 1 week. Certain species of ticks, however, can transmit systemic diseases such as Rocky Mountain spotted fever and Lyme disease. Rocky Mountain spotted fever, transmitted by dog ticks, is characterized by severe headache, rash, high fever, and extreme exhaustion. Lyme disease is caused by a spirochete found in deer ticks that is transmitted into the victim after the tick is attached for 36 hours. Of the 300,000 cases of Lyme disease diagnosed annually, the majority occur in the northeast and upper Midwest regions of the United States. Most

acute stages of Lyme disease are heralded by skin rash and influenza-like symptoms. The rash appears first as a papule at the bite site and may become an enlarged circle with a clear center called a “bull’s-eye rash” or *erythema migrans*. Tender urticarial lesions appear 3–30 days after the bite.¹² If left untreated, complications such as neurologic symptoms, cardiac disturbances, musculoskeletal symptoms, and arthritis may occur. Early diagnosis and prompt treatment by a health care provider are essential to prevent development of these serious manifestations.

Chiggers

Chiggers, or red bugs, live in shrubbery, trees, and grass. A common myth is that chiggers burrow into the skin and stay there. After attaching to the skin, usually around the edges of tight-fitting clothing, the larvae secrete a digestive fluid that causes cellular disintegration of the affected area, clusters of red papules, and intense itching. This fluid also causes the skin to harden and form a tiny tube in which the chigger remains to feed until engorged. It then drops off and changes into an adult.⁹

Spiders

Although all species of spiders are venomous, most are unable to penetrate the skin because their fangs are too short or too fragile. The black widow, brown recluse, and hobo spiders are three major exceptions. Deaths from spider bites are rare, but symptoms can be serious. Reactions to black widow bites includes erythema or a halo-shaped lesion, delayed intense pain, muscle spasms, abdominal disturbances, fever, chills, and dyspnea. Most brown recluse bites result in just a local reaction with itching and erythema. These bites, however, can progress into a necrotic ulceration, particularly in fatty areas of the body. Hobo spider bites typically present with a moderate to severe, slow-healing wound.¹³ If a spider bite is suspected but cannot be confirmed, the wound area should be monitored for these symptoms.

Complications of Insect Bites

Secondary bacterial infection of insect bites can occur if skin of the affected area is abraded from scratching. Skin infections, such as impetigo, may be a complication of insect bites. These infections may appear as yellow crusting, purulent drainage, and/or significant redness and swelling of the skin around

the bite.

Treatment of Insect Bites

Specific nonprescription external analgesics are labeled for use in treating minor insect bites.

Treatment Goals

The goals of self-treating insect bites are to relieve symptoms and prevent secondary bacterial infections.

General Treatment Approach

Application of an ice pack wrapped in a washcloth may provide sufficient relief of the pain and irritation of bites from mosquitoes, chiggers, bedbugs, or fleas. The ice pack is applied to the affected area for up to 10 minutes, with at least a 10-minute rest between applications. If this treatment does not work, applying an external analgesic to the site should relieve symptoms. Patients should be advised to avoid scratching the bite. Prevention of future insect bites also is important.

Self-treatment of insect bites with a nonprescription product is appropriate if the reaction is confined to the site of the bite and the patient is younger than 2 years. No effective nonprescription product is available to treat scabies. Patients with bites from ticks and spiders require medical referral because of possible systemic effects. [Figure 37–1](#) outlines treatment of insect bites and lists exclusions for self-treatment.

Nonpharmacologic Therapy

Nondrug measures include the two methods of preventing insect bites: avoiding insects and using repellents. Specific measures are listed in the box “Patient Education for Insect Bites” (see the section “Patient Counseling for Insect Bites.”)

Avoidance of Insects

Recommendations for avoiding insects are included in the box “Patient

Education for Insect Bites.”

Use of Insect Repellents

Insect repellents are useful in preventing bites from insects such as mosquitoes, fleas, and ticks, but these products are not effective in repelling stinging insects. Selection of an insect repellent should be based on product ingredients, concentration, preferred formulation, anticipated type and length of exposure, and patient-specific considerations. Most commercial products contain *N,N*-diethyl-*m*-toluamide, commonly called DEET, in concentrations ranging from 5% to 100%. DEET is considered to be the most efficacious repellent. Other insect repellent ingredients include synthetic chemicals such as 3-[*N*-butyl-*N*-acetyl]-aminopropionic acid, ethyl ester (IR3535), and picaridin, as well as plant-based components such as oil of lemon eucalyptus (OLE) (p-methane-3,8-diol [PMD]); catnip oil; and 2-undecanone. Examples of available insect repellents and their ingredients are included in [Table 37–1](#).

TABLE 37–1 Selected Nonprescription Insect Repellents

Trade Name	Primary Ingredient(s)
Cutter Skinsations Insect Repellent Pump Spray	DEET 7%; aloe vera; vitamin E
Cutter Sport Insect Repellent	DEET 15%
OFF! Deep Woods Sportsmen Insect Repellent I Pump Spray	DEET 98.25%
OFF! ACTIVE Insect Repellent I	DEET 15%
OFF! FamilyCare Insect Repellent II	Picaridin 5%
OFF! Deep Woods Insect Repellent Towelettes	DEET 25%
Skin So Soft Bug Guard Plus IR3535 Gentle Breeze SPF 30 Lotion	IR3535 7.5%; SPF 30 sunscreen
Skin So Soft Bug Guard Plus Picaridin Aerosol Spray	Picaridin 10%
Repel Plant-Based Lemon Eucalyptus Insect Repellent Pump Spray	Oil of lemon eucalyptus 30%
Repel Insect Repellent Sportsmen Max Formula Aerosol	DEET 40%
Repel Insect Repellent Mosquito Wipes	DEET 30%
Coleman Insect Treatment Gear & Clothing Aerosol Spray	Permethrin 0.5%

Trade Name	Primary Ingredient(s)
Sawyer Fisherman's Formula	Picaridin 20%

Key: DEET = *N,N*-Diethyl-*m*-toluamide.

***N,N*-Diethyl-*m*-Toluamide (DEET)**

The exact mechanism of action for DEET is not fully known. Similar to other repellents, DEET only repels insects from biting; it does not kill insects. When applied to skin or clothing, the volatile repellent releases vapors that tend to discourage the approach of insects.

Repellents, available in sprays, solutions, creams, wipes, and other forms, are applied as needed to skin or clothing according to package directions, usually no more frequently than every 4–8 hours. Concentrations less than 30% are preferable for children, and use of DEET insect repellents on children younger than 2 months should be discouraged.¹⁴ Products with DEET concentrations ranging from 10% to 35% provide adequate effect and sufficient protection for adults in routine situations, with concentrations of 20% or higher recommended to prevent tick bites. Concentrations greater than 50% do not offer any additional protection, but they may have a longer repellent effect. Unfortunately, products with such concentrations also may be associated with a higher incidence of skin reactions. Table 37–2 provides a summary from the Environmental Protection Agency, as well as other sources, regarding the application and safe use of DEET products.^{14–18}

TABLE 37–2 Guidelines for Safe Use of DEET
• Read and follow all directions and precautions on the product label. • Use just enough repellent to cover exposed skin and/or clothing. Do not use product under clothing. • Do not apply product over cuts, wounds, or irritated skin. • Do not apply product to hands or near eyes and mouth; apply in small amounts around ears. • To apply to face, spray product on hands first, and then rub on face. Do not spray product directly onto face. • Do not allow young children to apply this product. • Avoid overapplication of repellent. • Do not spray product in enclosed areas.

- Avoid inhalation of repellent.
- When sunscreen needs to be used in conjunction with a repellent, apply sunscreen first followed by the repellent.
- Product may damage synthetic fibers and plastics.
- Use of this product may cause skin reactions in rare cases.
- After returning indoors, wash treated skin with soap and water.
- Wash treated clothing before wearing it again.

Key: DEET = *N,N*-Diethyl-*m*-toluamide; EPA = Environmental Protection Agency.

Source: [References 11–14](#).

Although rare, skin irritation can occur after application of DEET-based insect repellents, with occlusion of the application area possibly contributing to skin rashes or eruptions. Central nervous system reactions, including seizures, ataxia, hypotension, encephalopathy, and angioedema, have been reported in association with improper use or ingestion.^{14,16,18} The Food and Drug Administration (FDA) advises against the use of products that combine insect repellents and sunscreen.¹⁹ Sunscreen products require more frequent applications compared with insect repellents; therefore, use of combination products can increase the risk of excessive DEET absorption.^{16,18} These products are considered safe if used appropriately, even in women who are pregnant or breastfeeding. [Table 37–2](#) lists warnings and precautions for use of DEET.

Other Insect Repellents

Alternative products include citronella, OLE, soybean oil, cedar oil, lavender oil, tea tree oil, garlic, and scented moisturizers in mineral oil (e.g., Skin-So-Soft). These products generally have been found to be less effective than DEET as repellents against mosquitoes, particularly with regard to length of action. Picaridin, an alternative to DEET, is being promoted as being less odorous and less irritating to skin.¹⁴ OLE should not be used in the “pure” form because its effects have not been studied. OLE and DEET provide similar protection against malaria, but OLE’s effect does not last as long. In addition, OLE should be avoided in children younger than 3 years.¹⁸ Limited information is available

regarding the safety and efficacy of catnip oil and 2-undecanone. Insect repellents containing permethrin 0.5% are designed for use only on clothing and camping equipment; they can effectively repel mosquitoes, ticks, and flies.¹⁴

Pharmacologic Therapy

External analgesics, such as local anesthetics, topical antihistamines, hydrocortisone, and some counterirritants, are approved for treating pain and itching associated with insect bites. These agents are not approved for use in children younger than 2 years.

Topical skin protectant agents may be used to reduce inflammation and promote healing. First-aid antiseptics and antibiotics can help prevent secondary infections (see [Chapter 41](#)).

Systemic antihistamines often are used in treating itching related to insect bites, but this use is not a label indication. [Chapter 11](#) discusses systemic antihistamines in detail.

Local Anesthetics

Local anesthetics such as benzocaine, pramoxine, benzyl alcohol, lidocaine, dibucaine, and phenol are approved in topical preparations for relief of itching, irritation, and pain caused by insect bites.

Local anesthetics cause a reversible blockade of conduction of nerve impulses at the site of application, thereby producing loss of sensation. Phenol exerts topical anesthetic action by depressing cutaneous sensory receptors.

Topical preparations containing local anesthetics are available as creams, ointments, aerosols, and lotions. These products generally are applied to the bite area up to 3–4 times daily for no longer than 7 days.

Local anesthetics are relatively nontoxic when applied topically as directed, and systemic absorption typically does not occur. However, allergic contact dermatitis may occur. Compared with other local anesthetics, pramoxine and benzyl alcohol do not commonly cause adverse effects and exhibit less cross-sensitivity. Dibucaine, a common allergen, may cause systemic toxicity if excessive absorption occurs. Convulsions, myocardial depression, and death

have been reported from systemic absorption.²⁰ Phenol solutions of concentrations less than 2% are irritating and may cause sloughing and necrosis of skin, but the concentration of phenol in nonprescription products ranges from 0.5% to 1.5%. Nonprescription products containing phenol should not be applied to extensive areas of the body, especially under compresses or bandages because of the risk of skin damage and systemic absorption.²¹ Products containing phenol should be avoided in pregnant patients and children.

Topical Antihistamines

Topical antihistamines exert an anesthetic effect by depressing cutaneous receptors and are approved for temporary relief of pain and itching related to minor insect bites.²² Products are available in several topical dosage forms; they are generally applied to the bite area up to 3–4 times daily for no longer than 7 days. Diphenhydramine hydrochloride in concentrations of 0.5%–2% is the agent used in most products that contain a topical antihistamine.²²

Although absorption occurs through skin, topical antihistamines generally are not absorbed in sufficient quantities to cause systemic adverse effects, even when applied to damaged skin. Systemic absorption is of more concern when these products are used over large body areas, especially in young children. Topical antihistamines can cause photosensitivity and hypersensitivity reactions; continued use of these agents for 3–4 weeks increases the possibility of contact dermatitis.

Counterirritants

Low concentrations of the counterirritants camphor and menthol are used in some topical analgesic products. [Chapter 7](#) discusses these agents in more detail. These products generally are applied to the bite area 3–4 times daily for up to 7 days.

Camphor

At concentrations of 0.1%–3%, camphor depresses cutaneous receptors, thereby relieving itching and irritation by exerting an anesthetic effect. However, camphor-containing products can be very dangerous if ingested. Patients should be warned to keep these products out of children's reach.

Menthol

In concentrations of <1%, menthol depresses cutaneous receptors and exerts an analgesic effect. Menthol is considered a safe and effective antipruritic when applied to the affected area in concentrations of 0.1%–1%.

Hydrocortisone

Hydrocortisone 1% topical preparations are indicated for temporary relief of minor insect bites. A wide variety of topical hydrocortisone dosage forms are available and should be applied as directed to the bite area 3 or 4 times daily for up to 7 days. [Chapter 35](#) provides additional information about topical hydrocortisone.

Skin Protectants

Medications such as zinc oxide, calamine, and titanium dioxide are applied to insect bites mainly in the form of lotions, ointments, and creams. These agents act as protectants and tend to reduce inflammation and irritation. Zinc oxide works as a mild astringent with weak antiseptic properties.²³ Zinc oxide and calamine also absorb fluids from weeping lesions. FDA considers nonprescription drugs containing zinc oxide and calamine to be safe and effective in concentrations of 1%–25%. These preparations should be applied to the affected area as needed. They have minimal adverse effects and are recommended for adults, children, and infants. Although its mechanism of action is similar to that of zinc oxide, titanium dioxide's safety and effectiveness have not been determined by FDA.

Product Selection Guidelines

Sensitization, specifically contact dermatitis, can occur with use and overuse of local anesthetics. Pramoxine and benzyl alcohol have a low incidence of adverse effects. Dibucaine and phenol have the most potential for adverse effects, especially if systemic absorption occurs from improper application.

Adverse effects and systemic absorption generally are not a concern with short-term use of the topical antihistamine diphenhydramine hydrochloride. Its prolonged use, however, can cause allergic or photoallergic contact dermatitis. Similarly, short-term use of hydrocortisone usually does not cause adverse effects or clinically significant systemic absorption. Patients with

scabies, bacterial infections, or fungal infections should not use hydrocortisone without medical supervision because it can worsen or mask these disorders. Camphor-containing products can be very dangerous if ingested, making them an inappropriate choice for use in children. Patients must understand that topical antipruritics and anesthetics should not be used for more than 7 days unless their health care provider specifically advises such use.

The patient's preference of dosage forms also should guide product recommendations. **Table 37–3** lists selected trade-name products in various dosage forms.

TABLE 37–3 Selected Nonprescription External Analgesic Products for Insect Bites and Stings	
Trade Name	Primary Ingredient(s)
Local Anesthetics	
Itch-X Gel/Pump Spray	Pramoxine HCl 1%; benzyl alcohol 10%
Lanacane First Aid Aerosol Spray 2-in-1 Fast Acting Pain Relief	Benzocaine 20%; benzethonium chloride 0.2%
Solarcaine Pain Relieving Aerosol Spray	Lidocaine 0.5%; aloe, vitamin E
Topical Antihistamines	
Benadryl Itch Stopping Cream	Diphenhydramine HCl 2%; zinc acetate 0.1%
Benadryl Itch Stopping Gel, Extra Strength	Diphenhydramine HCl 2%
Counterirritants	
Blue Star Ointment	Camphor 1.24%
Sarna Anti-itch Lotion Original	Camphor 0.5%; menthol 0.5%
Corticosteroids	
Aveeno Active Naturals Anti-Itch Maximum Strength Cream	Hydrocortisone 1%; aloe vera
Cortizone-10 Intensive Healing Anti-Itch Cream	Hydrocortisone 1%
Cortizone-10 Easy Relief Liquid	Hydrocortisone 1%; aloe vera

Trade Name	Primary Ingredient(s)
Combination Products	
Aveeno Anti-Itch Concentrated Lotion	Pramoxine HCl 1%; calamine 3%; dimethicone
Benadryl Extra Strength Anti-Itch Cooling Spray	Diphenhydramine HCl 2%, zinc acetate 0.1%
Caladryl Clear Lotion	Pramoxine HCl 1%; zinc acetate 0.1%; camphor
Campho-Phenique Gel	Camphor 10.8%; phenol 4.7%; eucalyptus oil
Chigarid External Analgesic	Camphor 2.6%; phenol 1.5%; menthol 0.1%; eucalyptus oil 0.5% in collodion
StingEze Insect Bite Relief	Benzocaine 5%; phenol 1.35%, camphor
Sting-Kill Swabs	Benzocaine 20%; menthol 1%

Assessment of Insect Bites: A Case-Based Approach

The type of insect that inflicted the patient's injury should be determined first. Patients with suspected spider or tick bites require a medical referral because of the risk of complications. For other insect bites, the seriousness of the reaction should be evaluated before a nonprescription product or nondrug measure is recommended. If a nonallergic reaction is present, the appropriate external analgesic for symptomatic relief should be recommended. Recommending a skin protectant to reduce irritation and inflammation or to prevent secondary bacterial infection is appropriate.

Patient Counseling for Insect Bites

Counseling for insect bites includes an explanation of how to treat the injury and how to prevent recurrences. Nondrug measures and proper use of recommended nonprescription products should be explained. The explanation should include potential adverse effects of these agents, plus signs and symptoms that indicate the injury needs medical attention. The time to improvement will vary depending on the type of insect bite and individual patient characteristics. Appropriate use of insect repellents to prevent further

bites also should be discussed. The box “Patient Education for Insect Bites” lists specific information to provide patients.

Evaluation of Patient Outcomes for Insect Bites

Follow-up should occur after 7 days of self-treatment. The patient should be advised to seek medical attention if symptoms such as redness, itching, and localized swelling worsen during treatment, or if the patient develops secondary infection, fever, joint pain, or lymph node enlargement. Medical attention also is necessary for symptoms that persist after 7 days of treatment.

Algorithm: Insect Bites

FIGURE 37–1 Self-care for insect bites. Key: AH = Antihistamine; D/C = discontinue; OTC = over-the-counter. Source: [References 4, 11, and 13.](#)

Insect Stings

Pathophysiology and Clinical Presentation of Insect Stings

Venomous insects such as honeybees, wasps, hornets, yellow jackets, and fire ants belong to the order Hymenoptera. They attack their victims to defend themselves or to kill other insects. The injected venom contains allergenic proteins and pharmacologically active molecules. Because venom contents vary within the Hymenoptera order, venom is discussed here in general terms.¹³

Most people will complain of pain, itching, and irritation at the site following an insect sting, but they generally will have no systemic symptoms. Individuals who are allergic to insect stings may experience hives, itching, swelling, and burning sensations of the skin. Although anaphylaxis is rare, those with severe allergies may experience a fall in blood pressure, light-headedness, chest tightness, dyspnea, and even loss of consciousness. These reactions may appear as soon as 10–15 minutes but no later than 6 hours after the sting.

Patients who receive multiple stings, such as from Africanized bees, may experience a toxic reaction with responses similar to anaphylaxis. Insect stings also may lead to delayed local inflammation 1–2 weeks after the sting.²⁴

Wild Honeybees, Wasps, Hornets, and Yellow Jackets

Wild honeybees are found most commonly in the western and midwestern United States; they usually nest in hollow tree trunks. Because the honeybee stinger is barbed, it remains embedded in the skin, even after the bee pulls away or is brushed off, and continues to inject venom. The venom from honeybees may cause a greater release of histamine compared with venom of other stinging insects.²⁵ Paper wasps, hornets, and yellow jackets are found more commonly in the southern, central, and southwestern United States. Paper wasps tend to nest in high places, under eaves of houses, or on branches of high trees, whereas hornets prefer to nest in hollow spaces, especially hollow trees. Yellow jackets, considered the most common stinging culprits, usually nest in low places, such as burrows in the ground, cracks in sidewalks, or small shrubs.²⁵ The stinging mechanism of wasps, hornets, and yellow jackets resembles that of the honeybee, except their stingers are not barbed. Their stingers can be withdrawn easily after venom is injected, enabling them to sting repeatedly.⁷

Patient Education for Insect Bites

The objectives of self-treatment for insect bites are (1) to relieve swelling, pain, and itching; (2) to prevent scratching that may lead to secondary bacterial infection; (3) to monitor for infections transmitted by ticks; and (4) to prevent future insect bites. For most patients, carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

Nondrug Measures

- Apply ice pack promptly to bite area to reduce swelling, itching, and pain.
- Avoid scratching the affected area; keep fingernails trimmed and clean.

- Remove ticks with tweezers by grasping the tick's head and gently pulling; the head should be removed. Keep the removed tick in a sealed container for future identification in case of systemic symptoms. After removal of the tick, clean the affected area with rubbing alcohol or soap and water to disinfect the skin.
- Do not wear rough, irritating clothing over bite area.

Preventive Measures

- To prevent exposure, cover as much skin as possible with clothing and socks, and cuff clothing around ankles, wrists, and neck. Clothing may be treated with permethrin to deter biting insects.
- Avoid swamps, dense woods, and dense brush that harbor mosquitoes, ticks, and chiggers.
- Keep pets free of pests.
- Remove standing water from around the home to reduce breeding areas for mosquitoes.
- Limit the amount of time spent outside at dawn and dusk.
- Use barriers such as window screens and netting.
- Apply insect repellent according to package recommendations to repel biting insects (see [Table 37–2](#)); these repellents do not deter stinging insects.
- To prevent transmission of scabies, avoid close, physical contact with infected individuals.

Nonprescription Medications

Topical Analgesics

- Use an external analgesic to relieve the pain and itching of insect bites. The choice of medications includes local anesthetics, topical antihistamines, counterirritants, and hydrocortisone.
- These products can be applied to the bite area 3–4 times daily. Do not use on children younger than 2 years. Do not use longer than 7 days.
- Note that local anesthetics can cause sensitization. If these agents are preferred, pramoxine and benzyl alcohol are less likely to cause

adverse effects.

- Do not use dibucaine in large quantities, particularly over raw surfaces or blistered areas. Such use could cause myocardial depression, convulsions, or death.
- Do not apply phenol to extensive areas of the body or under compresses and bandages. Such application increases the possibility of skin damage or systemic absorption.
- Do not use topical diphenhydramine longer than the recommended 7 days. Prolonged use can cause hypersensitivity reactions or systemic effects.
- Do not use hydrocortisone on scabies, bacterial infections, or fungal infections without a medical recommendation. Hydrocortisone can mask or worsen these disorders.
- Do not allow children to ingest camphor-containing products. Camphor is toxic when ingested.

Skin Protectants

- If a medication is needed to reduce irritation or inflammation, use a skin protectant such as zinc oxide or calamine.
- Apply protectant to affected area as needed up to 4 times daily.
- Some insect bite products contain external analgesics and skin protectants.

When to Seek Medical Attention

- Seek medical attention if the condition worsens during treatment or if symptoms persist after 7 days of topical treatment.
- Patients who were bitten by ticks or spiders or have scabies should seek medical attention promptly.

Fire Ants

Fire ants, imported from South America early in the 20th century and now found in the southeastern United States, live in underground colonies and form large raised mounds. Some ants only bite, whereas others bite and sting simultaneously; however, the bite is believed to cause the reactions. Fire ant

bites cause intense itching, burning, vesiculation, tissue necrosis, and anaphylactic reactions in hypersensitive individuals. The reaction to the bites initially leads to formation of pustules and may progress to ulcerated lesions.¹³

Treatment of Insect Stings

Although labeling of nonprescription products for insect-related injuries mentions only “insect bites” as an indication, it is generally accepted that FDA had intended the term to also cover insect stings.

Treatment Goals

The goal of self-treating insect stings is to relieve the itching and pain of cutaneous nonallergic reactions. Allergic or toxic reactions require immediate medical attention.

General Treatment Approach

Removal of the stinger followed by application of an ice pack in 10-minute intervals is the first step in treating insect stings. Application of topical hydrocortisone, local anesthetic, skin protectant, antiseptic, or counterirritant to the sting site is appropriate if the reaction is confined to the site and if no exclusions for self-treatment apply.¹³ Patients may benefit from oral diphenhydramine 25–50 mg per dose.²⁵ [Figure 37–2](#) lists exclusions for self-treatment and outlines the treatment of insect stings.

Algorithm: Insect Strings

FIGURE 37–2 Self-care for insect stings. Key: AH = Antihistamine; D/C = discontinue; OTC = over-the-counter. Source: [Reference 13](#).

Avoiding future insect stings can prevent an individual from developing allergic reactions to stings. If symptoms of an allergic reaction develop, emergency treatment should be administered, and the patient should seek medical attention. Patients with severe allergic reactions should be advised to wear a bracelet or carry a card identifying the nature of the allergy. They also should contact their primary care provider about carrying an injectable form of epinephrine.

Nonpharmacologic Therapy

Prompt application of cold packs to the sting site in 10-minute intervals helps to slow absorption of the venom and to reduce itching, swelling, and pain. Removal of the honeybee's stinger and venom sac, which are usually left in the skin, is important. The patient should remove the stinger before all venom is injected; approximately 2–3 minutes are needed to empty all contents from the honeybee's venom sac. The patient should not use tweezers or squeeze the sac because rubbing, scratching, or grasping it releases more venom. Scraping away the stinger with a fingernail or the edge of a credit card minimizes the venom flow. After the stinger is removed, an antiseptic, such as hydrogen peroxide or alcohol, should be applied.

Measures to avoid attracting stinging insects are included in the box "Patient Education for Insect Stings," which can be found in the section "Patient Counseling for Insect Stings."

Pharmacologic Therapy

The section "Treatment of Insect Bites" discusses the following topical products approved for treatment of insect bites and, by inference, insect stings: local anesthetics, topical antihistamines, counterirritants, hydrocortisone, and skin protectants.

Product labels for systemic antihistamines do not include treatment of itching associated with insect stings as an indication, even though these products are often used for this purpose.

Complementary Therapies

Meat tenderizer has been used on insect stings to "break down" proteins in venom. Ammonia and baking soda have been used to "neutralize" venom in insect bites. These products may affect itching. Most reports of their success are anecdotal, however, and to date their effectiveness has not been determined.

Assessment of Insect Stings

The critical determination in assessing a patient with an insect sting is

whether the patient is allergic to the venom. Patients experiencing allergic reactions should be referred immediately for emergency medical attention.

Case 37–1 illustrates assessment of a patient who has an insect sting.

Patient Counseling for Insect Stings

The health care provider should advise the patient that local reactions to insect stings usually are transient, but that severe reactions to insect stings can occur if sensitization to the insect venom develops with repeated exposure. The symptoms of allergic reactions should be explained. Patients who have a known hypersensitivity to insect stings should have epinephrine injection available at all times for emergency self-treatment.

For nonallergic reactions to stings, the provider should recommend one or more topical medications to manage immediate symptoms. The patient should be advised about adverse effects and any contraindications. The box “Patient Education for Insect Stings” lists specific information that should be provided.

Evaluation of Patient Outcomes for Insect Stings

Follow-up for nonallergic reactions to insect stings should occur within 7 days. The patient should be advised to seek medical attention if symptoms of pain, itching, and localized swelling worsen during the treatment period or persist after 7 days of treatment. Symptoms of secondary infection or fever also warrant medical attention. Follow-up for patients who have allergic reactions should occur the same day, if possible.

Case 37–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient’s symptoms and medical	A 42-year-old man approaches the pharmacy counter to request assistance with a tick bite. He had been

Relevant Evaluation Criteria	Scenario/Model Outcome
history, including	walking in the park across the street when he noticed the tick attached to his right ankle.
a. description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	He has been walking in the park for the last 2 hours, so he believes the tick crawled onto his skin during that time. He does not feel any symptoms at this time. He appears anxious regarding possible consequences of the tick bite. He does not appear to have any other local or systemic symptoms.
b. description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	n/a. He denies applying insect repellent prior to his walk.
c. description of the patient's efforts to relieve the symptoms	He has not tried to remove the tick. He knows that it needs to be removed carefully, so he is requesting assistance.
d. patient's identity	Sam Newton
e. age, gender, height, and weight	42 years old, male, 72 in., 210 lb
f. patient's occupation	Artist
g. patient's dietary habits	Sam is well nourished. He does not follow any specific diet.
h. patient's sleep habits	He generally works late into the night and then sleeps until midday. Sleeps 6-7 hours a night.
i. concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	<i>Hypertension:</i> amlodipine 5 mg daily and atorvastatin 10 mg daily
	<i>Dyslipidemia:</i> benazepril 20 mg daily
	<i>Pain:</i> occasional use of nonprescription acetaminophen
j. allergies	Sulfa antibiotics (rash)
k. history of other adverse reactions	Rash to sulfa antibiotics occurred when he was little.

Relevant Evaluation Criteria	Scenario/Model Outcome
to medications	No other reactions noted.
I. other (describe) _____	n/a
Assessment and Triage	
2. Differentiate patient's signs/symptoms and correctly identify the patient's primary problem(s).	Sam appears to have been bitten by a tick on his right ankle while walking in the park.
3. Identify exclusions for self-treatment.	History of a tick bite
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Application of local anesthetic, topical antihistamine, counterirritant, antiseptic, or hydrocortisone, including the following: a. anesthetic: Lanacane First Aid 2-in-1 Aerosol Spray (benzocaine 20%; benzethonium chloride 0.2%) b. antihistamine: Maximum Strength Benadryl Cream/Spray (diphenhydramine 2%) c. counterirritant: Blue Star Ointment (camphor 1.24%) d. antiseptic: hydrogen peroxide or alcohol e. hydrocortisone: Cortizone-10 Cream (hydrocortisone 1%) (2) Refer Sam for immediate medical attention. (3) Recommend self-care until an HCP can be consulted. (4) Take no action.
Plan	

Relevant Evaluation Criteria	Scenario/Model Outcome
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Refer Sam for immediate referral to an HCP because the tick needs to be identified to ensure appropriate treatment is provided for possible infection.
6. Describe the recommended therapeutic approach to the patient or caregiver.	Refer Sam to his usual HCP or an urgent care center.
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"You need immediate treatment for this tick bite. Depending on the type of tick, you may need to start antibiotic therapy within 36 hours of the bite to prevent certain infections."
Patient Education	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	Criterion does not apply in this case.
Solicit follow-up questions from the patient or caregiver.	"How do I remove the tick?"
Answer the patient's or caregiver's questions.	Ticks need to be removed as soon as possible and carefully to ensure all parts of the mouth are extracted: • Use a set of fine-tipped tweezers. • Attach the tweezer tips to the tick right at the edge of the skin to grab as much of the tick as possible. • Pull the tick straight away from the skin. • Do not squeeze the body of the tick. • Clean the area with rubbing alcohol or soap and water after removing the tick. • Do not apply nail polish or petrolatum to the tick, or use heating methods such as a hot nail or hot match to kill or remove the tick. • Take the tick in a container or plastic bag to an HCP for identification of the specific type

Relevant Evaluation Criteria	Scenario/Model Outcome
	of tick to determine the appropriate therapy. Applying an appropriate insect repellent prior to future outdoor activities is recommended.
Evaluation of Patient Outcome	
9. Assess patient outcome.	Call the patient within 1-2 days to ensure that he was able to see an HCP and, if indicated, to start appropriate prophylactic treatment. If he has not sought medical attention, advise him of the importance of prompt treatment to prevent complications from the tick bite.

Key: n/a = Not applicable; HCP = health care provider.

Patient Education for Insect Stings

The objectives of self-treatment for insect stings are (1) to relieve the swelling, pain, and itching of insect stings; (2) to monitor any reaction to the sting to determine whether an allergic reaction is developing; and (3) to prevent future insect stings. For most patients, carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

Nondrug Measures

- For honeybee stings, removing the honeybee stinger immediately is important. Scraping the stinger away with the edge of a credit card or fingernail is effective. Try not to squeeze or rub the stinger; these actions will actually release more venom.

- Apply an ice pack or a cold compress promptly to the sting site to help slow absorption of the venom. This action will reduce itching, swelling, and pain.
- Avoid scratching the affected area; keep fingernails trimmed and clean. Gloves or mittens may be used on small children during sleep to avoid unconscious scratching.
- To avoid attracting stinging insects, avoid wearing perfume, scented lotions, and brightly colored clothes; control odors in picnic and garbage areas; change children's clothing if it becomes contaminated with summer foods such as fruits; wear shoes when outdoors; and destroy nests of stinging insects near homes.
- If you are hypersensitive to stings, wear a bracelet or carry a card showing the nature of the allergy.

Nonprescription Medications

- For nonallergic stings, apply a topical nonprescription external analgesic such as a local anesthetic, topical antihistamine, counterirritant, or hydrocortisone to the affected site to relieve pain and itching. A skin protectant also can be recommended to prevent irritation and inflammation as well as to prevent secondary bacterial infection.
- These products can be applied 3–4 times daily for up to 7 days.

When to Seek Medical Attention

- If you have experienced previous severe reactions to insect stings, seek emergency medical care immediately. If a primary care provider has prescribed epinephrine or an oral antihistamine and you have it on your person, administer it according to the provider's instructions.
- Seek medical attention if you develop symptoms of an allergic reaction, such as hives, excessive swelling, dizziness, vomiting, or difficulty breathing.
- Seek medical attention if the pain and itching worsen during treatment or if they do not improve after 7 days of topical treatment.

Pediculosis

Pathophysiology and Clinical Presentation of Pediculosis

Lice are irritating pests, and lice infestations in the United States are common. Three types of lice that infest humans are head lice (*Pediculus humanus capitis*), body lice (*Pediculus humanus corporis*), and pubic lice (*Phthirus pubis*).

Head Lice

Head lice are the most common cause of lice infestation; outbreaks of lice infestation are common in places such as schools and daycare centers. Infestations most commonly are spread through direct head-to-head contact with an infected person. Sharing personal items such as caps, hairbrushes, and combs is unlikely to cause spreading.³ Outbreaks usually peak after the opening of schools each year, between August and November. All socioeconomic groups are affected. Head lice create problematic infestations, but they generally do not contribute to the spread of other diseases in the United States.²⁷

Head lice usually infest the head and live on the scalp (see [Color Plates](#), photographs 25A and B). A lice egg or nit is about 0.04 in. (1 mm) in diameter and is typically found within 0.16 in. (4 mm) of the scalp. Once hatched, the louse must begin feeding within 24 hours or it dies. The *nymph*, or newly hatched, immature louse, resembles an adult and matures within 8 to 9 days. Without treatment, this cycle may repeat every 3 weeks.²⁶ The bite of a louse causes an immediate wheal to develop around the bite, with a local papule appearing within 24 hours. Itching and subsequent scratching may result in secondary infection. Adult lice, which are about the size of a sesame seed, often are difficult to locate because they move when the hair is moved during inspection of the scalp. However, nits and nit casings generally can be spotted at the base of hair shafts when hair is parted for physical inspection. Hair inspections should focus on the crown of the head, near the ears, and at the base of the neck. The grayish nits blend in well with the hair, but nit casings (hatched nits) are a lighter color and are more easily located. Nits and nit

casings may be differentiated from dandruff, dirt, and so forth because of their firm attachment to the hair shaft. The presence of black powdery specks, lice feces, also is evidence of an infestation.

Body Lice

Body lice (or “cooties”) live, hide, and lay their eggs in clothing, particularly in the seams and folds of underclothes. They periodically attack body areas for blood feedings and can transmit infections such as typhus and trench fever. Body lice infestations generally occur in individuals who do not shower or change clothing frequently, such as the homeless.²⁷

Pubic Lice

Pubic lice or “crabs,” referring to their crab-like appearance, generally are transmitted through high-risk sexual contact, but they also may spread by way of toilet seats, shared undergarments, or bedding. The lice usually are found in the pubic area but may infest armpits, eyelashes, mustaches, beards, and eyebrows.²⁸

Treatment of Pediculosis

Nonprescription pediculicide agents, appropriate hair combing for nit removal, and home vacuuming and cleaning of personal items are primary treatments for lice infestation.²⁶

Treatment Goals

The goal of treating pediculosis is to rid the infested patient of lice by killing adult and nymph lice and by removing nits from the patient’s hair.

General Treatment Approach

A pediculicide is applied to the scalp for the designated amount of time to rid the patient of lice. The hair is then combed with a lice or nit comb to remove nits from the hair shaft; combing also will remove dead lice. Once rid of lice, patients should be instructed on how to avoid future infestations. [Figure 37–3](#) outlines treatment of lice infestations and lists exclusions for self-treatment.²⁶

Nonpharmacologic Therapy

Because none of the pediculicides kills 100% of lice eggs, the National Pediculosis Association recommends careful visual inspection of the hair for nits and combing with an FDA-approved nit comb, such as the LiceMeister comb; removal of nits is helpful in treating and controlling head lice.²⁹ The AirAllé (formerly called the LouseBuster) is a machine that applies heat to the hair and scalp to dehydrate and kill lice and nits. Preliminary evidence suggests this procedure kills more than 90% of nits.³⁰ Unfortunately, it is expensive and requires a certified technician to operate the machine.

Direct physical contact with an infested individual should be avoided, and articles such as combs, brushes, towels, caps, and hats should not be shared. However, use of borrowed protective head gear during sports or recreational activities should not be avoided because of fear of lice transmission. Clothing and bedding should be washed in hot water and dried in a clothes dryer to kill lice and their nits; an alternative to washing would be to seal contaminated items in a plastic bag for 2 weeks. Hairbrushes and combs should be washed in very hot water. Carpets, rugs, and furniture should be vacuumed thoroughly and regularly.²⁶ Use of insecticidal sprays on these items generally is not recommended because lice usually survive for less than 48 hours when not in contact with a host.²⁶ Given the increasing resistance to pediculicides, some patients are choosing to use nondrug therapy exclusively; these nondrug methods, specifically combing and vacuuming, can be effective, but they are labor intensive and tedious.³¹ Complete head shaving also has been used as a lice treatment, but the social stigma involved makes this a distasteful option. Body lice are controlled by appropriate body hygiene and frequent changing and appropriate laundering of clothing and bed linens.²⁸

Pharmacologic Therapy

Two nonprescription pediculicide agents are available for treating pediculosis: permethrins and synergized pyrethrins. Health care providers should be concerned about increasing resistance to the nonprescription pediculicides. Research published in 2016 reported that 42 states in the United States had lice with genetic mutations, indicating resistance to nonprescription pediculicides.³²

Synergized Pyrethrins

Synergized pyrethrins are approved for the treatment of head and pubic lice. Pyrethrins are synergized by addition of piperonyl butoxide. This agent limits the ability of lice to break down pyrethrins.

Pyrethrins block nerve impulse transmission, causing the insect's paralysis and death. As noted, piperonyl butoxide synergizes pyrethrins' insecticidal effect through inhibition of pyrethrin breakdown, increasing the insecticide levels within the louse to more toxic concentrations.^{26,33} Excessive contact time or occlusion of the scalp after product application may increase skin absorption of topical pyrethrins.

Pyrethrins, in concentrations ranging from 0.17% to 0.33%, generally are used in combination with 2%–4% piperonyl butoxide. This combination is considered an effective pediculicide when applied topically as shampoos, foams, solutions, or gels. The medication is applied to the affected area for 10 minutes; then the treated area is rinsed or shampooed as recommended. Combing with a lice comb should follow the treatment. This treatment is repeated in 7–10 days to kill any remaining nits that have since hatched. The drug should not be applied more than twice in 24 hours.²⁶

When applied according to directions, pyrethrins have a low order of toxicity. Most adverse reactions are cutaneous and include irritation, erythema, itching, and swelling.^{26,33} Contact with eyes and mucous membranes should be avoided.

Individuals allergic to pyrethrins or chrysanthemums should not use this agent; ragweed-sensitive individuals risk cross-sensitivity. Pyrethrins should not be used in children younger than 2 years.

Permethrin

Permethrin, a synthetic pyrethroid, is available as a nonprescription cream rinse for treating head lice only. Permethrin acts on the nerve cell membrane of lice. It disrupts the sodium channel, delaying repolarization and causing paralysis and death of the parasite.

When permethrin is applied, an estimated less than 2% is absorbed, after which the agent is metabolized.

The 1% cream rinse is applied in sufficient quantities to cover or saturate washed hair and scalp. It is left on the hair for 10 minutes before rinsing; the hair is then combed with a lice comb. The rinse has residual effects for up to 10 days; therefore, retreatment in 7–10 days is not required unless active lice are detected.

Primary adverse effects, which can occur in up to 10% of the patient population, include transient pruritus, burning, stinging, and irritation of the scalp. Contact with eyes and mucous membranes should be avoided.

Permethrin is contraindicated in patients who are sensitive to pyrethrins or chrysanthemums. Permethrin should not be used on infants younger than 2 months.

Pharmacotherapeutic Comparison

When treatment involves a single application of a pediculicide, permethrin is more effective than the pyrethrin and piperonyl butoxide combination. However, to date, no significant difference exists in effectiveness of these agents when treatment consists of two applications. A comprehensive meta-analysis is ongoing.²⁶

Product Selection Guidelines

Preparations that contain synergized pyrethrins may be used on children ages 2 years and older, but they should be used in pregnancy and lactation only if prescribed by a health care provider. Synergized pyrethrins may be recommended for treating pubic lice. For treatment of head lice, synergized pyrethrins or permethrin may be selected on the basis of preferred dosage form, desire for single application, or patient allergies and sensitivities. [Table 37–4](#) lists selected trade-name products containing available nonprescription pediculicide agents.

TABLE 37–4 Selected Nonprescription Pediculicides and Alternative Therapies

Trade Name	Primary Ingredient(s)
A-200 Lice Killing Shampoo	Pyrethrins 0.33%; piperonyl butoxide 3%

Trade Name	Primary Ingredient(s)
RID Lice Killing Shampoo	Pyrethrins 0.33%; piperonyl butoxide 4%
Nix Lice Killing Cream Rinse	Permethrin 1%
Pronto Lice Killing Shampoo	Pyrethrins 0.33%; piperonyl butoxide 4%
LiceMD	Dimethicone 100%
Vamousse Lice Treatment	Natrum muriaticum 2X (HPUS)
Licefreee Spray	Natrum muriaticum 2X (HPUS)
Clearlice Shampoo	Proprietary blend: enzyme proteins; neem oils; <i>Wrightia tinctoria</i> ; tea tree oil; <i>Acorus calamus</i> ; peppermint oil; <i>Cocos nucifera</i> ; Natrum muriaticum

Alternative Therapies

A variety of alternative therapies have been used to eliminate lice infestations; however, none are approved by FDA. Lice enzyme shampoos, which claim to break down the lice exoskeleton, are being promoted as an alternative to traditional pediculicides. A product containing 10% tea tree oil and 1% lavender oil applied weekly for 3 weeks was more effective at eradicating lice than a pyrethrin/piperonyl butoxide product applied twice (1 week apart).³⁴ Tea tree oil must be used with caution because of potential significant allergic reactions and possible liver toxicity.³⁵ Other oil-based products such as petroleum jelly and mayonnaise also are being used on the basis of the theory that they impair lice respiration; however, these products are not very effective and most likely only slow the movement of lice.^{26,35} Dangerous alternative treatments such as gasoline and kerosene always should be avoided because of their flammability and potential for toxicity.²⁶

A homeopathic remedy containing *Natrum muriaticum*, also known as sodium chloride, works by drying out lice and their eggs. In a randomized trail

including 42 pediatric patients with head lice, the sodium chloride spray demonstrated efficacy superior to that of permethrin.³⁶ These products are applied to sections of dry hair for 15 minutes followed by combing with a nit comb. **Table 37–4** lists specific sodium chloride products available in the United States.

Battery-operated louse combs with oscillating teeth (MagiComb and RobiComb) also are available; although they claim to kill lice, no published studies that evaluate their effectiveness are available. Use of the electronic combs should be avoided in patients with pacemakers or histories of seizures.²⁶

Emerging Therapies

A new potential treatment under study uses dry-on, suffocation-based pediculicide (DSP) lotions. The Nuvo method, the first DSP product to be tested, contains Cetaphil Gentle Skin Cleanser and is a nontoxic lotion that “shrink-wraps” lice.³⁷ It is applied to hair and dried with a hairdryer to form a shrink-wrap film over hair and lice. The lotion covers breathing holes, suffocating the louse. One study suggests that suffocation products may be more effective than pyrethrins/piperonyl butoxide; however, additional research is needed.³⁴

Dimethicone 100% gel also has been shown to cure pediculosis while causing less irritation than traditional therapy. Furthermore, dimethicone works by coating the lice and irreversibly immobilizing them within 5 minutes of application.³⁸

Assessment of Pediculosis: A Case-Based Approach

In many cases of pediculosis, visual inspection of the scalp will verify the presence or absence of head lice or nits. Similarly, presence of body lice can be determined by identifying adult lice and nits in seams of clothing. If a patient does not want such an inspection or if lice/nits have not been confirmed by another health care provider, a pediculicide should not be recommended. When the disorder is confirmed, the appropriate pediculicide should be recommended. If resistance to pyrethrins or permethrin has been reported in the region, patients should be referred to a health care provider for a

prescription pediculicide. However, because of the cost of prescription products for head lice, an alternative therapy can be recommended.²⁶

Case 37–2 illustrates assessment of a patient who has a head lice infestation.

Patient Counseling for Pediculosis

Control of pediculosis requires both pharmacologic and nonpharmacologic intervention. The health care provider should reassure parents of children with head lice that the condition is not the result of poor hygiene. Patients with confirmed head or pubic lice infestations should be counseled on which product is best for the situation and how to use the product properly; preventive measures also should be discussed. Additional information regarding patient counseling for pediculosis can be found in the box “Patient Education for Pediculosis.”

Algorithm: Pediculosis

FIGURE 37–3 Self-care for pediculosis. Key: D/C = Discontinue. Source: Reference 26.

Case 37–2

Relevant Evaluation Criteria	
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of	A frantic woman comes into the pharmacy asking about OTC options

Relevant Evaluation Criteria	
symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	for head lice. She says that her 7-year-old daughter has just returned from summer camp complaining of an “itchy” scalp that started a day or so ago. Her daughter admits to sharing another girl’s cap the day before leaving camp and denies any itching prior to that event. Upon further inspection, the woman noticed clusters of small red bumps that cover the child’s scalp and appear on the base of the neck. She also noticed tiny, light-colored “dandruff looking things” attached firmly to the hair shaft. She reports her daughter’s complaints are itching and mild scalp pain.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient’s symptom(s)	The woman explains that she had just picked up her daughter from camp when she noticed her daughter scratching her head. She inspected her daughter’s scalp once they returned home. She was not able to comment on any precipitating or exacerbating symptoms because the daughter was at camp.
c. Description of the patient’s efforts to relieve the symptoms	The woman has taken all of her daughter’s clothes out of her suitcase and placed them in a large plastic bag to be washed when she goes home.
d. Patient’s identity	Caroline Davis
e. Patient’s age, gender, height, and weight	7 years, female, 45 inches, 52 lb
f. Patient’s occupation	Second-grade student
g. Patient’s dietary habits	Mother says that Caroline usually eats a well-balanced diet.
h. Patient’s sleep habits	Caroline usually sleeps about 9 hours per night.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	None

Relevant Evaluation Criteria	
j. Allergies	Chrysanthemums (rash), amoxicillin (rash)
k. History of other adverse reactions to medications	None
l. Other (describe) -----	n/a
Assess	
2. Differentiate patient's signs/symptoms and correctly identify the patient's primary problem(s).	Patient has observable nit casings and small red papules throughout the scalp and base of the neck. Patient has recently returned from summer camp and reports sharing head ware with another child, a common occurrence associated with head lice infestation.
3. Identify exclusions for self-treatment (Figure 37-3).	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Purchase nit comb for nit observation and removal. (2) Use pyrethrins 0.33% with piperonyl butoxide 4% shampoo products. (OTC permethrin product should be avoided due to chrysanthemum allergy.) (3) Refer patient to an HCP. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem,	Pyrethrins 0.33% with piperonyl butoxide 4% shampoo products

Relevant Evaluation Criteria	
taking into account patient preferences.	
6. Describe the recommended therapeutic approach to the patient or caregiver.	• “Your daughter appears to have head lice and is eligible for self-treatment. I recommend a nonprescription product to kill the head lice.” • “Use a pyrethrin shampoo first: – Apply enough to wet the dry hair and scalp. – Allow the treatment to stay for 10 minutes. – Lather the shampoo throughout the hair and then rinse. – Use a nit comb to remove dead lice and eggs. – Repeat this in 7–10 days if lice or nits are detected.” “When using the nit comb, part the hair into segments, and comb each segment to ensure thorough removal of the nits.”
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	“This product should kill the head lice.”
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	“To prevent the lice from spreading, make sure to follow all directions on the product labeling, and wash or seal items that your daughter may have come in contact with.”
Solicit follow-up	“What else should I do to help prevent the spread of lice?”

Relevant Evaluation Criteria	
questions from the patient or caregiver.	
Answer the patient's or caregiver's questions.	• "Wash hairbrushes, combs, and toys that have come in contact with your daughter in water that is 130°F (39.4°C) or higher for 10 minutes." • "Clothes, bedding, and towels used by your daughter also should be washed in water that is 130°F (39.4°C) or higher. They should be dried on the hottest dryer setting possible." • "Items that cannot be washed should be sealed in plastic bags for 2 weeks" • "Vacuum living areas regularly." • "Visually inspect hair and scalp before, during, and after treatment for lice or nits."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	• "If head lice are still present after two rounds of treatment, you will need to contact your primary care provider to see if you can obtain a prescription product." • Advise the parent that significant skin irritation or exposure of eyes to pediculicides require medical attention.

Key: HCP = Health care provider; OTC = over the counter.

Patient Education for Pediculosis

The objectives for self-treatment of pediculosis are (1) to rid the body of lice and nits and (2) to implement measures to prevent future infestations. For most patients, carefully following product instructions and the self-

care measures listed here will help ensure optimal therapeutic outcomes.

Nondrug Measures

- Wash hairbrushes, combs, and toys of infested patients in water at a temperature of 130°F (39.4°C) or higher for 10 minutes.²⁰
- Use water at a temperature of 130°F (39.4°C) or higher to wash the clothes, bedding, and towels of infested patients. Dry the items on the hottest dryer setting that the fabric permits.²⁰
- Objects or clothing that cannot be washed should be sealed in plastic bags for the length of the louse's life cycle (2 weeks) so that it is unable to feed on a host.
- Avoid close physical contact with an infested patient; do not share articles such as combs, brushes, towels, caps, and hats.
- Vacuum living areas thoroughly and regularly during treatment period.
- Visually inspect the hair and scalp before, during, and after treatment for evidence of lice or nits.
 - Use a nit comb diligently to remove nits.
 - Part hair into segments and comb the hair in each segment. (Individual hairs can be trimmed if nit removal proves difficult.)

Nonprescription Medications

- Treatment of other family members should be determined on the basis of the presence of lice or nits and the family members' level of contact with the infested individual; unnecessary treatment should be avoided.
- Application steps for a pyrethrin shampoo include the following:
 - Apply sufficient quantity to wet the dry hair and scalp. (Foams should also be applied to dry hair.)
 - Allow the treatment to remain for 10 minutes.
 - Work the shampoo into a lather and then rinse thoroughly. (Remove foams with shampoo or soap and water.)
 - Use a nit comb to remove dead lice and eggs as described previously.

- Application steps for a permethrin cream rinse include the following:
 - Shampoo with regular shampoo, rinse, and towel dry hair.
 - Apply sufficient cream rinse to wet hair and scalp.
 - Allow the treatment to remain for 10 minutes; then rinse and towel dry.
 - Use a nit comb as described previously.
- Avoid contact of the pediculicide with eyes and mucous membranes.
- The pediculicide can cause temporary irritation, erythema, itching, swelling, and numbness of the scalp; itching should be relieved in a few days.
- For pyrethrin products, repeat entire process in 7–10 days; permethrin products can be used again in 7–10 days if lice or nits are detected. Because of treatment resistance, proper use of these products is required and overuse must be avoided.
- If desired, contact the National Pediculosis Association at www.headlice.org or 1-617-905-0176 for information about treatment of lice infestations.
- If pediculicides are ruled out as a treatment option, alternative products such as citronella, lemon eucalyptus oil, soybean oil, cedar oil, lavender oil, tea tree oil, garlic, and scented moisturizers in mineral oil (e.g., Skin-So-Soft) may be tried.

When to Seek Medical Attention

- Significant skin irritation or excessive exposure of eyes or mucous membranes to pediculicides.
- If symptoms of lice infestation persist after the second treatment.
- If resistance to pyrethrins or permethrin has been reported in the region.

Evaluation of Patient Outcomes for

Pediculosis

Follow-up of lice infestations should occur within 10 days. If signs of lice infestation persist after a second application of a pediculicide, the patient should be advised to seek medical attention. Overuse of these products should be discouraged, and use of nonpharmacologic control measures should be emphasized.³¹

Key Points for Insect Bites and Stings and Pediculosis

- Insect stings and bites cause local irritation, inflammation, swelling, and itching; a cold pack may be applied to reduce local symptoms.
- For relief of the itching and pain resulting from insect bites, topical nonprescription preparations that contain local anesthetics, antihistamines, hydrocortisone, or counterirritants can be used in patients ages 2 years and older.
- In hypersensitive people, anaphylactic reactions may pose serious emergency problems; these patients require immediate medical attention.
- Suspected spider bites should be referred; nonprescription treatments are not appropriate. If possible, the spider should be sealed in a container for identification.
- A tick should be removed by grasping it near the head with tweezers and gently pulling to cause the tick to release from the skin. The patient should be monitored for systemic effects such as Lyme disease and Rocky Mountain spotted fever.
- Appropriate use of insect repellents containing DEET will help prevent bites from mosquitoes, ticks, and fleas.
- Exposure to mosquito bites warrants monitoring the patient for

symptoms of mosquito-borne viruses.

- Nondrug measures are an important component in treatment of lice infestation.
- Available nonprescription pediculicides contain either synergized pyrethrins or permethrin.
- Pediculicides are designed for initial treatment and retreatment in 7–10 days; hair should be combed with a nit comb after treatment.
- If resistance to pyrethrins and permethrin has been reported in the region, patients should be referred to a medical provider for a prescription pediculicide, or an alternative therapy should be recommended.

Chapter 38: Acne

Authors: Jamie L. Woodyard, Chelsea M. Baker

Acne, also known as *acne vulgaris*, is an inflammatory skin disease affecting 40–50 million people in the United States.¹ The Latin word *vulgaris* means “common” or “affecting the masses.” The 2010 Global Burden of Disease study ranks acne as the eighth most prevalent disease worldwide.² Acne is a disorder of the pilosebaceous glands, resulting in lesions most commonly found on the face. Locations for extrafacial lesions include the back (52%), chest (30%), lower back (22%), shoulders and arms (16%), and neck (8%).³

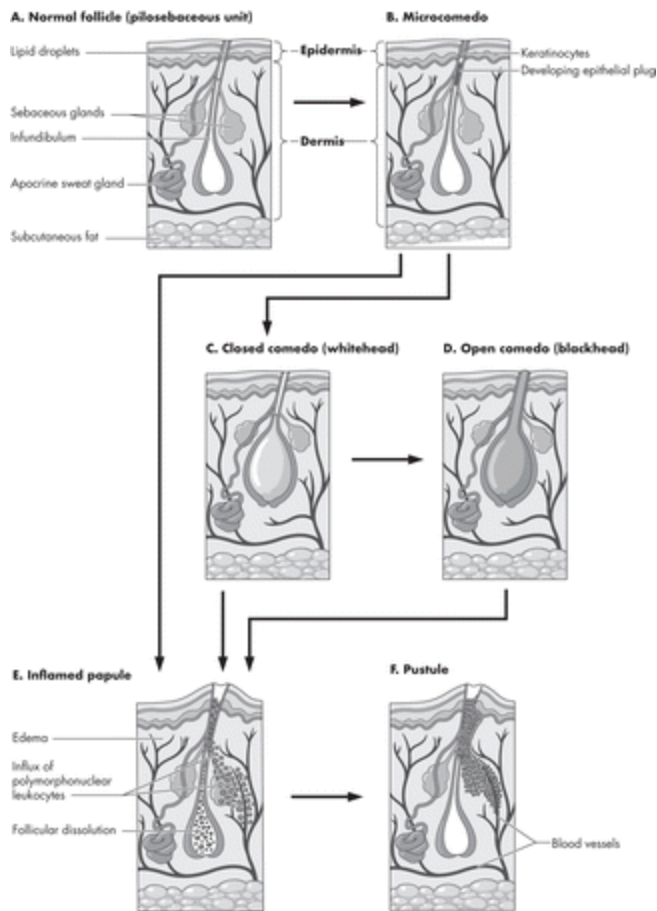
Acne is most common during adolescence. Cordain et al. have described acne as a universal disease that affects 79%–95% of adolescents in Westernized societies.⁴ The age for peak prevalence of acne is 14–17 years in girls and 16–19 years in boys. Although clinical improvement typically is seen starting at 20–25 years of age, the condition may persist in 7%–17% of affected persons, with an even higher rate of nearly 24% for women. Late-onset acne, defined as emergence of acne signs and symptoms in persons older than 25 years, accounts for 8% of the cases.⁵ Acne persists in 1% of men and 5% of women after the age of 40.⁵

Acne was once considered a disease of teenagers.⁶ The onset of acne correlates with the onset of puberty; however, acne may occur in adolescents younger than 12 years.⁶ Recently, the prevalence of acne in children has increased, with rates of 28%–61% reported for those 10–12 years of age. According to Eichenfield et al., acne also is common in preadolescents (ages 7–12 years).⁶ Additionally, acne has been observed in children 4–7 years of age.⁴

The effect of acne on certain health indicators should not be overlooked. Associations have been shown between acne and lower self-esteem.⁷ Acne may have a negative impact on quality of life similar to that experienced by patients with asthma or epilepsy.⁷ Additional associated morbidity may include scarring, depression, and anxiety. In 2019, the manufacturing industry for nonprescription acne treatments reported revenue of \$425.3 million.⁸ In 2017, sales of nonprescription acne products totaled \$607 million.⁹ In the United States, direct and indirect costs related to acne treatment were reported at \$3 billion.¹⁰

Pathophysiology of Acne

Acne is the result of several pathologic processes that occur within the pilosebaceous unit located in the *dermis*, or middle layer of the skin (Figure 38–1A). Each unit consists of a hair follicle and associated sebaceous glands and is connected to the skin surface by a duct (*infundibulum*) lined with epithelial cells through which the hair shaft passes. The sebaceous glands produce sebum, which normally functions to protect the skin from light and to retain moisture. Sebum possesses an antibacterial property that is both pro- and anti-inflammatory and is involved in the wound healing process.¹¹ The sebaceous gland acts as an endocrine organ and responds to changes in androgens and hormones similar to the action of the hypothalamic–pituitary–adrenal axis; hence, the sebaceous gland has been called the “brain of the skin.” Corticotropin-releasing hormone (CRH) influences the sebaceous glands’ endocrine function.¹² CRH is the primary hormone involved in neuroendocrine and behavioral responses to stress. In acne-prone skin, CRH is found throughout the sebaceous glands and has been associated with the immune and inflammatory processes that lead to stress-induced acne.¹¹



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FIGURE 38–1 Pathogenesis of acne. (Source: Adapted with permission from Fulton JE, Bradley S. The choice of vitamin A acid, erythromycin, or benzoyl peroxide for the topical treatment of acne. *Cutis*. 1976;17(3):560.)

The etiology of acne is multifactorial. In addition to the intricate pathophysiology of this condition, genetics, diet, and gender play important contributory roles. In a study of 200 patients with postadolescent acne by Ebede et al., 50% of the subjects reported at least one first-degree family relative with acne.¹³ More research is needed to explore the role of genetics in acne.³ Recent literature has increasingly focused on the role of environmental factors, such as diet, in the etiology of acne. Cordain et al. studied acne prevalence in young people, including adolescents, in non-Westernized populations.⁴ One study cohort comprised 1200 Kitava Islanders (Papua New Guinea), including 300 subjects 15–25 years of age, who were examined every 6 months over a period of 843 days: no case of acne was observed in this cohort. The investigators also observed 115 Aché (indigenous Paraguay) subjects, 15 of

whom were 15–25 years of age, for more than 2 years and again found no cases of active acne.⁴ These authors concluded that the absence of contributing environmental factors, especially diets characterized by high glycemic loads with corresponding insulin spiking, typical for Western populations, may be key in this virtual immunity to acne and suggested that clinicians should look toward these differences to treat the condition.⁴

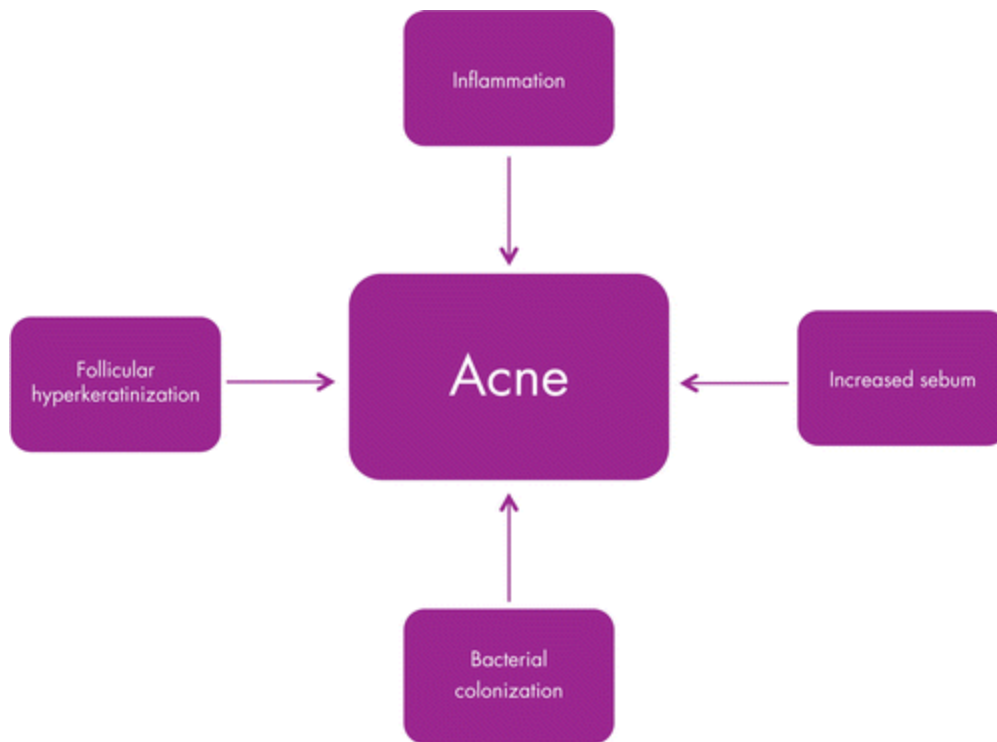
Additional epidemiologic studies have correlated acne with the Western diet.¹⁴ The non-Western diets, with low glycemic loads, also featured lower consumption of dairy products, alcohol, cereals, oil, sugar, and salt.¹⁴ Foods with a high glycemic index elevate plasma concentrations of insulin, which regulates insulin-like growth factor-1 (IGF-1) and IGF-binding protein, promotes unregulated tissue growth, and enhances androgen synthesis.¹⁵ Hormones such as androgens and IGF-1 act on sebaceous glands and keratinocytes.¹⁵ Dietary milk also causes a rise in the serum level of IGF-1 through substantial elevation of blood glucose and serum insulin levels.¹⁴ Melnik examined the role of mTORC1 (mammalian target of rapamycin complex 1) as a nutrient-derived signal involved in the exacerbation of acne through diet.¹⁶ The mTORC1 signal is activated with consumption of foods with a high glycemic index and high intakes of fat, dairy, and meat. These foods are characteristic of those found in the Western diet.¹⁶ The mTORC1 kinase integrates signals of cellular energy, growth factors (insulin, IGF-1), and protein-derived signals, predominantly leucine, which is provided in large amounts by milk proteins and meat, with resultant increases in androgen and sebum production, respectively, which further perpetuates the pathogenesis of acne.¹⁶ As noted by Melnik, the role of diet in acne pathogenesis is still controversial, but the discovery of nutrient signaling pathways, such as mTORC1, helps explain the link between diet and acne exacerbation.¹⁶ Currently, no specific dietary changes are recommended in the management of acne, although emerging data show evidence that diets consisting of high-glycemic-index foods may be associated with acne.¹⁷

Pathologic factors involved in the development of acne are (1) sebum production by the sebaceous gland, (2) follicular colonization by *Cutibacterium acnes* (previously known as *Propionibacterium acnes*), (3) alteration in the keratinization process, and (4) release of inflammatory mediators in the skin.¹²

The rise in androgenic hormones coincides with the start of puberty and the appearance of acne. Conversion of testosterone to dihydrotestosterone stimulates an increase in the size and metabolic activity of sebaceous glands.

The excess sebum serves as a breeding ground for *C. acnes* as the comedo (whitehead or blackhead) develops. Increases in androgen levels also are responsible for abnormal follicular desquamation within the infundibulum. Sebum includes several matrix metalloproteinases.¹² This group of enzymes have a prominent role in inflammatory matrix remodeling and proliferative skin disorders.¹³ Medications targeting these enzymes are being developed for acne treatment. Examples of these medications are adapalene and prescription antibiotics such as tetracyclines and macrolides.¹⁸ Evidence also indicates that follicular keratinocytes release interleukin-1, which may stimulate comedo formation. Specifically, the skin of people without acne has been shown to exhibit inflammatory responses that occur before the hyperproliferation of keratinocytes in acne.¹² The understanding of the pathophysiology of acne is still evolving. A landmark study from 2003 demonstrated that the pathogenesis of acne begins with an inflammatory process, rather than with hyperkeratinization and comedogenesis.¹⁹ This study also found that inflammatory responses are a key component in the early stages of acne lesion formation.¹⁹

Figures 38–1 and 38–2 illustrate the complex interplay of the pathophysiologic processes in acne. Hyperproliferation of keratinocytes results in cell cohesion and formation of a plug that blocks the follicular orifice. This plug distends the follicle to form a *microcomedo*, the initial pathologic lesion of acne (Figure 38–1B).²⁰ As more cells and sebum accumulate, the microcomedo enlarges and becomes visible as a *closed comedo*, or *whitehead*, a small, pale nodule beneath the skin surface (Figure 38–1C). If the contents of the plug cause distention of the pore's orifice, the plug will protrude, creating an *open comedo*, or *blackhead*. The lesion is named for the presence of melanin and oxidation of lipids upon exposure to air.



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FIGURE 38–2 Pathophysiology of acne. (Source: [References 5 and 20.](#))

Currently, no exact and clear explanation has emerged for the pathogenesis of acne.²¹ Newly recognized potential pathophysiologic factors include T-helper cells, acne subtype, and nutritional status.²¹ Acne is no longer believed to be caused by a proliferation of *C. acnes*, as studies have demonstrated similar amounts of *C. acnes* in the follicles of both unaffected persons and those with acne.^{22–24} More recent research has focused on the effects of a subset of *C. acnes* strains with enhanced pathogenicity and the interplay of *C. acnes* with other bacterial species, particularly *Staphylococcus epidermidis*, on the skin microbiota equilibrium.^{22,25–30} Greater understanding of *C. acnes* strains and the role of other bacteria in the etiopathogenesis of acne may assist in the development of alternative treatment options.

Clinical Presentation of Acne

Information continues to evolve around the presentation of acne. Through production of lipases, *C. acnes* breaks down sebum into highly irritating free

fatty acids. As a result of the irritation and inflammation, localized tissue destruction occurs. Toll-like receptors (TLRs) are mammalian proteins that act as a vital regulator of host responses to infection.¹² Research shows cytokine induction by *C. acnes* occurs through TLR-2, which stimulates inflammatory lesions. In acne, TLR-2 invokes a significant inflammatory response as well as cellular apoptosis and tissue injury.³¹ Redness and inflammation in and around the follicular canal are the hallmarks of a *papule* (Figure 38–1E). A *pustule* (Figure 38–1F) possesses those same qualities but has visible purulence in the center of the lesion. *Nodules* result from disruption of the follicular wall and release of its contents into the surrounding dermis.²⁰

Several factors contribute to the exacerbation of existing acne and cause periodic flare-ups (“flares”) of acne in some patients (Table 38–1).^{32–34}

TABLE 38–1 Etiologic Subtypes of Acne With Exacerbating Factors	
Etiologic Subtype	Description
Acne cosmetica	Development of noninflammatory comedones on the face, chin, and cheek caused by occlusion of the pilosebaceous unit by oil-based cosmetics, moisturizers, pomades, or other health and beauty products
Acne excoriee (excoriated)	A form of acne caused by constant picking, squeezing, or scratching at real or perceived lesions, which worsens the appearance of the skin
Acne mechanica	Local irritation or friction from occlusive clothing, headbands, helmets, or other friction-producing devices
	Excessive contact between face and hands, such as resting the chin or cheek on the hand
Chloracne	An acneiform eruption caused by exposure to chlorine compounds
Drug-induced acne	<i>More common:</i> anabolic steroids, bromides, corticosteroids, corticotropin, isoniazid, lithium, phenytoin
	<i>Less common:</i> azathioprine; cyclosporine; disulfiram; phenobarbital; quinidine; tetracycline; vitamins B ₁ , B ₆ , B ₁₂ , and D ₂
Hormone-induced acne	Hormonal alterations, specifically increased androgen levels induced by medical conditions, pregnancy, or medications
Hydration-induced acne	Hydration-induced decrease in size of pilosebaceous duct orifice and prevention of loosening of comedones caused by high-humidity environments

Etiologic Subtype	Description
	and prolonged sweating
Occupational acne	Exposure to dirt, vaporized cooking oils, or certain industrial chemicals, such as coal tar and petroleum derivatives
Stress- and extreme emotion-induced acne	May induce expression of neuroendocrine modulators and release of CRH, which play a role in centrally and topically induced stress of the sebaceous glands and possibly progression of acne

Key: CRH = Corticotropin-releasing hormone.

Source: [References 32–34](#).

Until recently, acne was categorized as noninflammatory or inflammatory (see [Color Plates](#), photographs 26 and 27). Noninflammatory lesions included open or closed comedones. Inflammatory lesions included papules, pustules, and nodules. Subsequently, however, Do et al. discovered that although 54% of inflammatory lesions were preceded by comedones, 28% developed in normal skin. Furthermore, it was demonstrated that cellular inflammatory lesions could occur at every stage of acne. According to these authors, noninflammatory lesions should be considered comedones, and probable new evidence supports occurrence of the inflammatory process at every stage of acne.³⁵ Acne lesions typically are found on the face, chest, upper back, and upper arms.²⁰ Affected women in their 30s and 40s not uncommonly have lesions concentrated on the chin and along the jaw line.³⁶ At clinical presentation, the patient may exhibit one or more types of lesions. Acne severity is defined by the number and type of acne lesions³⁷; however, no consensus has emerged on an optimal grading system.^{17,38} [Table 38–2](#) describes a commonly used acne grading system to assess acne severity.³⁷

TABLE 38–2 Grading and Classification of Acne

Mild	Moderate	Severe
Few erythematous papules	Many erythematous	Extensive pustules, erythematous

Mild	Moderate	Severe
and occasional pustules mixed with comedones	papules and pustules and prominent scarring	papules, and multiple nodules on an inflamed background

Source: [Reference 38](#).

If acne lesions persist beyond the affected person's mid-20s or first appear in the mid-20s or later, the clinical manifestations may signal rosacea, rather than acne. Differentiation between the two conditions is necessary because the treatment of rosacea, although similar to that for acne, has unique elements. In rosacea, erythema and telangiectasias or facial flushing on the cheeks are characteristic, but no comedones are present.³⁸

In addition to the negative psychosocial impact of acne, physical scarring can be a complication of the condition.³⁹ Scarring manifests as (1) hypertrophic areas and keloids caused by increased tissue formation and (2) a loss of skin resulting in so-called ice pick, boxcar, or rolling scars.³⁹ In an observational study of patients with and without scarring, Kircik concluded that the subjects with scarring exhibited an initial cellular response to acne that was weaker and less effective throughout the resolution of lesions. These patients also experienced a later influx of macrophages and increased inflammatory responses that resulted in persistent inflammatory hyperpigmentation.¹⁹

Treatment of Acne

In most cases, acne is self-limiting and can be controlled to a variable degree. Adherence to therapeutic regimens will reduce the frequency and severity of clinical manifestations and minimize or prevent scarring. Because acne persists for long periods, treatment must be long-term, continuous, and consistent.

Treatment Goals

Although lesion elimination is ideal, a realistic primary treatment goal is a

decrease in the number and severity of lesions. Additional goals include prevention of future lesions, scar formation, and hyperpigmentation, along with improvement in quality of life.

General Treatment Approach

Patients and health care providers should identify any exacerbating factors for the acne ([Table 38–1](#)). It also is imperative for providers to classify the type of acne ([Table 38–2](#)), to allow selection of the most appropriate therapeutic option(s).³⁸ Once the subtype of acne has been established, treatment should be initiated and adherence to medication therapy encouraged.¹² A major global problem with acne treatment is lack of adherence.⁴⁰

Gollnick has described a general three-pronged treatment approach for acne: (1) eliminating visible lesions that occur during the acute phase of acne, (2) maintaining treatments that prevent relapse, and (3) implementing adjunctive procedures to treat scarring or other complications.⁴⁰

Nonpharmacologic Therapy

An important first step in self-care management of acne is to eliminate or avoid exacerbating factors ([Table 38–1](#)). Patients should be advised to cleanse the skin with a mild soap or nonsoap cleanser no more than twice daily, as use of abrasive products and excessive cleansing may worsen acne.

Another essential self-care measure is staying well hydrated. Dehydration may lead to an increase in inflammatory chemicals in the cell and cause dysfunction in the natural desquamation process of the stratum corneum. According to Decker and Graber, normal skin has a pH of 5.3–5.9. Washing the face with harsh soaps that increase the pH by 2 or more units can cause skin dryness and create an environment supporting growth of *C. acnes*.⁴¹ Facial toners may decrease a tendency to oily skin and will help remove makeup and traces of dirt. However, patients should not overuse such products because they can cause increased skin irritation.⁶ Patients also could consider dietary changes by eliminating or cutting back on foods with a high glycemic index to determine whether the acne improves or remains the same.⁴²

Physical Treatments

Physical treatments include light therapies and mechanical therapies such as use of scrubs, cleansing cloths, brushes, and heating devices (Table 38–3).⁴¹ Comedo extraction also is an example of a physical treatment.¹⁷ A wide range of self-applied, acrylate glue–based material strips can aid in the extraction of impacted comedones.⁴¹ The American Academy of Dermatology working group for the guidelines on care and management of acne notes that professional comedo extraction is a useful adjunct to the overall acne regimen and often results in immediate improvement; however, evidence for effectiveness of physical therapies is limited.¹⁷

TABLE 38–3 Description of Physical Treatments	
Implement	Treatment
Brushes	The oscillating motion of the brush is used to deeply cleanse the skin while removing makeup. The impact of this treatment has not been clinically evaluated.
Cleansing cloths	Cloths are less abrasive than scrubs while providing conditioning and exfoliation of the skin.
Cosmetic adhesive pads	Pads were developed to remove adherent corneocytes, dirt, oil, or to loosen open comedones from the skin.
Heating devices	Heating devices are marketed to treat acne vulgaris by directly contacting the lesion. A beneficial effect deriving from exposure to heat and phototherapy has been described.
Light therapy	Examples are visible light, pulsed dye laser, and photodynamic therapies. The most abundant evidence exists for photodynamic therapy in treating acne. A photosensitizer is applied to the affected skin for 15 minutes to 3 hours.
Scrubs	Abrasion opens closed comedones and prevents their progression; however, the abrasive effects of such products can damage the integrity of the skin.

Source: [Reference 41](#).

The U.S. Food and Drug Administration (FDA) has approved several light-based

therapies for the treatment of acne. These treatments target reduction of *C. acnes* and disruption of sebaceous gland function. *C. acnes* bacteria produce porphyrin compounds during normal metabolism. Porphyrins absorb visible light at a variety of wavelengths, which excites the porphyrin compound, causing the formation of oxygen and free radicals.⁴³ The oxygen radicals are thought to destroy *C. acnes* organisms by damaging lipids in their cell walls.¹² Light therapy currently is considered a modality to be used in conjunction with traditional pharmacologic therapy for acne. Additional research on regimens that include light therapy as a standard of treatment is needed.¹⁷

Pharmacologic Therapy

Recent evidence indicates that nonprescription topical therapy offers benefits and should have a role in the treatment of acne.⁴¹ Topical therapy is the standard of care in acne treatment.⁴⁴ Health care providers should be familiar with the nonprescription products available for treatment of acne.

Adapalene

On July 8, 2016, FDA approved adapalene gel 0.1% (Differin Gel) for nonprescription treatment of acne. It is the first new ingredient approved for acne treatment since the 1980s and the first full prescription-strength retinoid to become available without a prescription.⁴⁵ Adapalene is a first-line topical drug for acne treatment.^{20,45} Its mechanism of action differs from that of other available nonprescription acne agents. Adapalene appears to modulate epithelial cell differentiation, keratinization, and inflammation and is preferred for treatment of comedonal acne because of its mechanism of action.^{17,46} Patients should follow all label directions for this product. A thin layer of the product should be applied to affected, intact skin areas once daily at bedtime. The affected areas should be protected from sun exposure, as adapalene increases susceptibility to sunburn.⁴⁶

Redness, scaling, dryness, itching, and burning are the most common adverse effects of adapalene, but they often diminish after the first month of therapy. Acne may worsen during the first weeks of therapy because this medication affects lesions that are not yet visible on the skin. The full therapeutic effect of adapalene will become apparent after 8–12 weeks of treatment.⁴⁶ If acne-related signs and symptoms worsen or fail to abate in 3 months with proper use of the agent, patients should consult their primary care provider. In

addition, product users who experience allergic reactions, become pregnant, or are planning to become pregnant should discontinue use of adapalene and consult their primary care provider for other treatment options.⁴⁶

Benzoyl Peroxide

Benzoyl peroxide (BP) is the most common topical acne product available both with and without a prescription. BP has keratolytic and antibacterial properties against skin *C. acnes*.¹⁷ BP kills bacteria by introducing oxygen into the environment, thereby killing *C. acnes*, which can thrive only in an oxygen-free environment.²⁰

BP has been the mainstay of treatment for acne since the 1930s.⁴¹ In March 2010, FDA issued a final rule for topical acne drug products that included BP as a generally recognized as safe and effective (GRASE) active ingredient in nonprescription topical acne products.⁴⁷ BP had been classified as a non-GRASE ingredient since 1995 because of concern about benzoyl's weak mutagenic effect in vitro and BP's tumor promotion potential.⁴⁷ FDA later concluded that BP in concentrations of 2.5%–10% is a GRASE ingredient for acne on the basis of animal studies suggesting that BP is not carcinogenic or photocarcinogenic.⁴⁷

One of the main benefits of BP is its ability to prevent or eliminate the development of treatment resistance by *C. acnes*, which has increased with the use of conventional antibiotics (e.g., macrolides, tetracyclines) over the past 3 decades.¹² Resistant strains have been found in 50% of acne patients who had close contact with a resistant organism.¹² *Close contact* is defined as exposure to those persons living in the same household with family members with acne. The use of BP in combination with antibiotics is recommended to minimize *C. acnes* resistance.¹² BP often is used in combination with other oral or topical antibiotics. In a 2009 literature review, BP was more effective than topical antibiotics such as clindamycin and erythromycin. In addition, BP in combination with either of these antibiotics was more effective and better tolerated than either of the antibiotics alone.¹²

Nonprescription formulations of BP are available in concentrations of 2.5%–10% as a gel, wash, or cream. Higher strengths of BP have the same antibacterial effects as for the lower strengths⁴¹ but may cause more skin irritation.⁴⁸ All new users of nonprescription acne products should test the product by

applying it sparingly to 1–2 small affected areas over the first 3 days. If discomfort does not occur, the product should be used according to label directions.⁴⁷

Avoidance of contact with clothes or hair is advised, as this product may cause bleaching. In addition, BP can cause photosensitivity, so avoidance of excessive sun exposure and use of a broad-spectrum sunscreen product with a sun protection factor (SPF) of 15 or higher are recommended. Minor improvement may occur with once-daily application of BP. The number of applications can be increased gradually to 2 or 3 times daily if needed. If excessive peeling or drying occurs, the frequency of application or the BP concentration should be reduced. Results have been seen in as few as 5 days or by week 3 of treatment. Maximum lesion reduction may occur after 8–12 weeks of use. Some patients may experience only mild erythema and scaling during the first few days, which usually subside within 1–2 weeks.

BP is recommended for mild acne in adults and pediatric populations (preadolescents and adolescents).⁶ Allergic contact dermatitis reactions, characterized by a sudden onset of erythema and vesiculation, are considered rare, with an occurrence rate of 1 in 500. A 2014 FDA Drug Safety Communication reported rare but serious allergic reactions to BP and salicylic acid that ranged from symptoms of local irritation to local and systemic hypersensitivity, including anaphylaxis.⁴⁸ FDA has not determined if the products' active ingredients, inactive ingredients, or both are responsible for these reactions. Use of BP products should be discontinued when an allergic reaction such as itching or development of hives occurs. Medical attention should be sought for manifestations of hypersensitivity reactions such as throat tightness, difficulty in breathing, a feeling of faintness, or swelling of the eyes, face, lips, or tongue.⁴¹ The box "Patient Education for Acne" presented later in the chapter lists other precautions for use of BP.

Other Nonprescription Acne Agents

Other FDA-approved nonprescription topical anti-acne ingredients include hydroxy acids in various strengths, sulfur 3%–10% (in single-ingredient products), and combinations of sulfur 3%–8% with either resorcinol 2% or resorcinol monoacetate 3%.⁴⁹

Hydroxy Acids

Keratolytic agents such as alpha hydroxy acids (AHAs) and beta hydroxy acids (BHAs) also are common nonprescription acne products. Hydroxy acids are considered less potent and often are used when patients cannot tolerate other topical acne products.⁴⁹ Some hydroxy acids have comedolytic properties and are moderately effective in the treatment of acne.⁴⁹

AHAs are natural exfoliating acids that occur in sugar cane, milk products, and fruits; the most common AHAs are glycolic, lactic, and citric acids, respectively.⁴⁰ AHAs are not able to penetrate the pilosebaceous unit to exert a comedolytic effect. AHAs are available in several nonprescription formulations in concentrations of 4%–10% or as prescription-only products in higher concentrations. In a study comparing BP with AHAs, BP demonstrated a superior effect at 8 weeks. Once acne is controlled, a light chemical peel with AHAs may be useful to help correct scarring and hyperpigmentation.¹² However, several treatments are needed, and the results are not long-lasting. The duration of dosing is once every 15 days for 4–6 months.¹⁷ **Table 38–4** lists contraindications to glycolic acid peels of which the health care provider should be aware.

TABLE 38–4 Glycolic Acid Peel Contraindications

Active infection or open wounds (herpes simplex, excoriations, open acne cysts)
History of abnormal scar formation or delayed wound healing
History of rosacea, seborrheic dermatitis, atopic dermatitis, psoriasis, vitiligo, active retinoid dermatitis
History of therapeutic radiation exposure
Isotretinoin therapy within the past 6 months
Lack of psychological stability and mental preparedness
Poor general health and nutritional status
Unrealistic expectations
<i>For medium and deep peels only:</i>
Medium-depth or deep resurfacing procedure within the past 3–12 months

Source: [Reference 17](#).

Polyhydroxy acids constitute a category of AHAs that have fewer adverse effects, such as irritation and stinging. They are marketed for patients with more clinical sensitivity and have moisturizing and humectant properties.³⁹ Lactobionic acid, a type of polyhydroxy acid, inhibits the breakdown of matrix metalloproteinase enzymes with sun exposure. This effect reduces “photoaging” of the skin.³⁹

Salicylic acid, often described as a BHA, is a comedolytic agent available as various nonprescription acne products in concentrations of 0.5%–2%.^{39,49} The comedolytic effect is concentration-dependent. Higher concentrations are used in prescription products and chemical peels.³⁹ Salicylic acid is a milder, less effective alternative to prescription agents such as topical retinoids.¹⁵ In cleansing preparations containing salicylic acid, this ingredient is considered an adjunctive agent. As a comedolytic, salicylic acid should be applied 1–3 times daily as needed. If dryness or peeling occurs, the frequency of application should be reduced to once daily or every other day.⁴² Salicylic acid is a phytohormone chemically similar to the active component of aspirin. It is important for health care providers to be aware of potential drug–drug interactions ([Table 38–5](#)) with the use of this agent. Salicylic acid is lipid-soluble and able to penetrate the pilosebaceous unit to produce a comedolytic effect.⁴⁹ Of note, with topical application of 2% salicylic acid, up to 20% of the preparation’s drug content can be absorbed in the skin. The degree of absorption depends on several factors, including the vehicle used, the pH of the drug, skin structure, the frequency of application, and whether or not an occlusive covering is used. A risk of salicylism or salicylic acid toxicity associated with topical application to extensive areas of the skin has been recognized, especially in children, who metabolize drugs differently. Accordingly, some patients will require additional monitoring, as well as possible dose adjustments of any maintenance medications, if the treatment regimen includes chronic use of salicylic acid or frequent widespread applications.¹⁷

TABLE 38–5 Drug–Drug Interactions With Salicylic Acid

Interacting Drug/Drug Class	Potential Interaction	Management
Anticoagulants	Increased anticoagulation	Use with caution and monitor closely.
Antidiabetic agents	Increased activity of glyburide; hypoglycemia	Monitor closely; use alternative acne agent, if possible.
Aspirin	Increased anticoagulation; increased serum level of potassium	Monitor closely; consider alternative agent.
Corticosteroids	Prednisone may increase renal clearance; increased risk of gastrointestinal tract ulceration	Monitor closely.
Diuretics	Increased serum level or effect of salicylates	Monitor closely.
Methotrexate	Increased serum level of methotrexate	Monitor closely.
Heparin	Decreased platelet adhesiveness and interference with hemostasis in heparin-treated patients	Monitor closely.
Uricosuric agents	Effect of probenemide, sulfinpyrazone, and phenylbutazone inhibited	Monitor closely.
Pyrazinamide	Pyrazinamide-induced hyperuricemia inhibited	Monitor closely; may consider alternative acne agent.

Source: [Reference 17](#).

Salicylic acid products also offer protection from the sun by inhibiting ultraviolet B (UVB) radiation–induced formation of “sunburn cells” occurring after exposure to UVB rays, which cause irreversible damage to cellular DNA, and by increasing the removal of UVB-induced *dimers* (premutagenic lesions) in skin.⁴⁹ However, patients using these products should continue to wear a broad-spectrum sunscreen with an SPF of 15 or higher to protect their skin from further sun damage. Use of BHA products is contraindicated in diabetic

patients or persons with poor blood circulation. Application of these products should be limited to the affected area, as use over extensive surfaces for prolonged periods may result in toxicity. Signs and symptoms of salicylate toxicity include nausea, vomiting, dizziness, hearing loss, tinnitus, lethargy, hyperpnea, diarrhea, psychological disturbances, inner ear damage, hypoglycemia, and hypersensitivity.⁴⁹ In 2014, FDA warned of potentially life-threatening hypersensitivity reactions for nonprescription anti-acne products containing salicylic acid or BP (see the section “Benzoyl Peroxide”).

Sulfur

Sulfur, precipitated or colloidal, is included in anti-acne products as a keratolytic and antibacterial in concentrations of 3%–10%.⁴⁹ Sulfur generally is accepted as effective in promoting the resolution of existing comedones, but with continued use it may have a comedogenic effect. Alternative forms of sulfur such as sodium thiosulfate, zinc sulfate, and zinc sulfide are not recognized as safe and effective.

Adverse effects with these products are rare but include noticeable odor and dry skin, depending on the formulation used.⁴¹ Sulfur often is combined with sodium sulfacetamide to mask the odor of sulfur in prescription drugs, and sulfur is combined with resorcinol in nonprescription medications for treatment of acne.⁴⁹

Sulfur/Resorcinol

Combinations of sulfur 3%–8% with resorcinol 2% or resorcinol monoacetate 3%, both of which enhance the effect of sulfur, are available in nonprescription acne products.^{41,49} These products function primarily as keratolytics, fostering cell turnover and desquamation. Resorcinol is not effective when used for monotherapy. However, it is believed to have antibacterial, antifungal, and keratolytic effects when used with other anti-acne products such as sulfur.⁴¹

Pharmacotherapeutic Comparison

Table 38–6 provides a comparison of the therapeutic properties of the major anti-acne products.

TABLE 38–6 Comparison of Properties for Nonprescription Topical Anti-Acne Agents

Agent	Property			
	Antibacterial	Comedolytic	Anti-inflammatory	Keratolytic
Adapalene 0.1%	No	Yes	Yes	Yes
Benzoyl peroxide 2.5%–10%	Yes	Yes	No	Yes
Salicylic acid 0.5%–2%	No	Yes	Yes	No
Sulfur 3%–10%	Yes	No	No	Yes
Resorcinol 2% with sulfur 3%–8%	Yes	No	No	Yes
Resorcinol monoacetate 3% with sulfur 3%–8%	Yes	No	No	Yes

Source: [References 6, 17, 40, 41, and 48](#).

Product Selection Guidelines

Product selection should be based on individual patient needs, skin type, and severity of acne. Nonprescription acne medications are indicated for mild acne. Skin cleansers and topical acne products are available in a variety of vehicles and strengths. Medicated cleansing products (bars and liquids) are less effective, as they leave little active ingredient residue on the skin. Generally, gels are the most effective formulations because they are astringents and remain on the skin the longest. Gels and solutions have a drying effect and may cause contact dermatitis. However, these dosage forms are not greasy and may be more beneficial in patients with oily skin. Creams and lotions generally are less irritating to the skin than gels and solutions.⁵⁰ They are acceptable alternatives to more effective gels and are recommended for dry or sensitive skin and for use during dry winter weather. Ointment vehicles are not used, because they are occlusive and tend to worsen acne. Patients should start with the lowest strength available and gradually increase the concentration to minimize irritating effects of the product. The product should be applied only once daily; if the applications are well tolerated with no

redness or skin irritation, the frequency of application may be increased to twice daily. **Table 38–7** lists selected nonprescription trade-name anti-acne products in these and other formulations.

TABLE 38–7 Selected Nonprescription Anti-Acne Products	
Trade Name	Primary Ingredient(s)/Component(s)
Retinoid Product	
Differin Gel, 15 g	Adapalene 0.1%
Benzoyl Peroxide Products	
Proactiv Repairing Treatment, 2 oz	Benzoyl peroxide 2.5%
Neutrogena Rapid Clear Stubborn Acne Cleanser, 5 oz	Benzoyl peroxide 10%
Clearasil Ultra Rapid Action Vanishing Treatment Cream, 1 oz	Benzoyl peroxide 10%
Salicylic Acid Products	
Neutrogena Oil-Free Acne Stress Control Power Cream Wash, 6 oz	Salicylic acid 2%
Clean & Clear Advantage Acne Spot Treatment, 0.75 oz	Salicylic acid 2%
Alpha Hydroxy Acid Products	
Alpha Hydrox AHA Soufflé 12% Glycolic AHA, 1.6 oz	Glycolic acid 12%
Gly Derm Face Lotion Lite Plus 10, 4 oz	Glycolic acid 10%
Alpha/Beta Hydroxy Acid Product	
M.D. Forté Skin Rejuvenation Hydra-Masque, 4 oz	Glycolic acid; salicylic acid
Polyhydroxy Acid Product	
NeoStrata Bionic Face Cream, 1.4 oz	Gluconolactone 8%; lactobionic acid 4%
Sulfur Product	
De La Cruz Sulfur Ointment 10% Acne Medication, 2.6 oz	Sulfur 10%
Sulfur/Resorcinol Product	

Trade Name	Primary Ingredient(s)/Component(s)
Adult Acnomel Tinted Cream, 1.3 oz	Resorcinol 2%; sulfur 8%
Physical Treatment Products	
Bioré Deep Cleansing Pore Strips	Comedo extraction strip
BlueMD Blue Light Therapy	Infrared LED lights
Garnier SkinActive Clean+ Refreshing Remover Cleansing Towelettes	Cleansing cloth
Olay Pro-X Advanced Cleansing System	Acne brush
Tanda Zap Acne Spot Treatment Device	Heat therapy

Key: LED = Light-emitting diode.

Many patients will use nonprescription medications in combination with prescription products to manage acne. Patients should be aware of current medications that may cause acne as well as potential drug interactions that may occur with nonprescription products. Product selection and adherence are important for the successful treatment and management of acne. Consultation with an appropriate health care provider is important for proper diagnosis and grading of acne. For example, women who experience acne related to hormonal imbalance may benefit more from correction of the imbalance with hormone therapy, such as oral contraceptives, whereas a peripubertal teenager or young adult may benefit more from recommendations for avoidance of comedogenic products and adherence to regimens based on nonprescription products such as BP.⁵⁰

Special Populations

In pregnant patients, acne may develop because of hormonal imbalances. In most cases, if pregnancy occurs during treatment with any acne medication, the medication should be discontinued and the obstetrician advised of current or previous product use because of the potential for teratogenic effects. Very

limited human data are available to describe the use of topical BP, sulfur, hydroxyl acids, and photodynamic therapy during pregnancy.⁵¹ (See the Preface for a detailed explanation of the pregnancy data.) Glycolic acid peels have not been rated for use in pregnancy. Use in pregnancy of any treatment options should be limited to clinical situations in which the potential benefit justifies potential risk to the fetus.

Acne occurs in all age groups, including the pediatric population. This population comprises neonates, infants, and young children. Most cases of infantile and neonatal acne are self-limiting; however, a differential diagnosis by appropriate health care providers, which may include a pediatric endocrinologist, is needed for treatment recommendations.⁶ Use of aspirin and aspirin-containing products, such as salicylic acid, in children or teenagers who have or are recovering from chickenpox or flulike symptoms should be avoided because of the risk of Reye syndrome. (See [Chapter 5](#) for further discussion of Reye syndrome.)

Complementary Medicine, Vitamins, and Vitamin Analogs

Tea tree oil is widely known for its antibacterial and antifungal properties. *Staphylococcus aureus*, a common pathogen found on the skin, is sensitive to tea tree oil. Tea tree oil also has anti-inflammatory properties.⁵² Terpinen-4-ol, the active ingredient in tea tree oil, has been suggested to suppress production of inflammatory mediators and inflammation.⁴¹ Topical tea tree oil has been shown to be effective at reducing lesion counts, but no robust conclusive studies have assessed its efficacy in acne.⁴¹

Oral zinc may be considered as an alternative to tetracyclines.^{12,41} Zinc is bacteriostatic against *C. acnes*, inhibits chemotaxis, and has shown effectiveness against severe acne. One study found that although zinc was 17% less effective than minocycline, it could be used as an alternative to tetracycline therapy, especially in the summer, because it does not cause phototoxicity. However, zinc's adverse effects of nausea, vomiting, and diarrhea have made it less desirable for acne therapy, with poor patient compliance due to these adverse effects limiting its use.^{41,49}

Vitamin A is a naturally occurring retinol that is transformed into several metabolites.⁴⁹ The metabolite retinoic acid is used in cosmetics to help

eliminate wrinkles and fine lines. Theoretically, retinol also should work against acne. However, few studies have emerged to validate this claim. Oral vitamin A or retinol may be beneficial in acne in doses up to 300,000 international units (IU) daily for women and 500,000 IU daily for men.⁴⁹ Common adverse effects include xerosis and cheilitis.

Nicotinamide, a water-soluble derivative of vitamin B₃, also is used for acne.⁴¹ Nicotinamide is an active form of niacin and has been postulated to be of benefit for the treatment of acne by several mechanisms of action: It is an anti-inflammatory that improves the texture of sun-damaged skin and also decreases sebum production.^{21,53} Data on nicotinamide's role in acne are limited, however, and more research needs to be conducted to assess its benefit for this condition.

Limited data are available on the safety and efficacy of other complementary and alternative therapies for their use in acne.¹⁷

Algorithm: Acne

FIGURE 38–3 Self-care for acne. Key: OTC = Over-the-counter.

Assessment of Acne: A Case-Based Approach

Assessment begins with the initial patient interview to define the condition. Physical assessment, which involves observing the affected area and further questioning of the patient as directed by the clinical findings, is the next step in evaluation. This process will determine whether the disorder is acne or another dermatologic condition with similar signs and symptoms. Physical assessment also will determine whether the severity of the condition precludes self-treatment ([Figure 38–3](#)). Before self-care is recommended, a review of current medication use, prescription and nonprescription, is necessary to reveal prescribed treatments for the disorder or use of medications known to cause acne ([Table 38–1](#)).

Cases 38–1 and 38–2 are examples of assessment of two different patients presenting with acne.

Patient Counseling for Acne

The success of the treatment regimen depends largely on the patient’s adherence. It is crucial for the health care provider to communicate the causes of acne, correct any misconceptions, and clearly explain the rationale for treatment. Patient buy-in will facilitate adherence and increase the likelihood of a successful outcome. Key patient factors are maturity and willingness to adhere to a skin care program that involves a continued daily regimen of washing affected areas and applying medication. Reassurance and emotional support often are necessary to reduce patient concern, as acne may only be controlled—not cured. The box “Patient Education for Acne” lists specific information to provide in patient counseling.

The internet is a source of supplemental information about acne in nontechnical language, including nonprescription drugs used to treat the condition, and treatment expectations. Selected sites are listed in [Table 38–8](#). If not copyrighted, online materials can be printed and given to the patient during consultation. If the material is copyrighted, the health care provider should instead provide the website address.

TABLE 38–8 Selected Websites for Acne Information	
Organization	Website
American Academy of Dermatology	www.aad.org
Acne.org	www.acne.org
U.S. Food and Drug Administration	www.fda.gov

Evaluation of Patient Outcomes for Acne

Although the patient may expect complete resolution of acne, a more realistic expectation for self-treatment is clinical improvement, defined by a decrease in both the number and severity of lesions. The health care provider should medically refer patients whose acne shows no improvement after 6 weeks of adherence to self-treatment or after 6 months of diet changes, or if a patient has moderate to severe acne. If some improvement is observed, the provider

may suggest monthly follow-up to monitor progress and adjust the self-treatment regimen as needed.

Case 38–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	A young woman comes to the pharmacy counter requesting a treatment option for acne. She expresses distress over her visible facial lesions: "I hate going to my dance classes because I feel people are staring at the pimples on my face." She has noticed a few yellowish pimples but states that most of the spots are red raised bumps. She reports that she has had occasional mild "breakouts" since her early teens but notes the condition has been worsening over the past 3 weeks.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	She states that her acne gets worse whenever she has a dance performance, which is nearly once a week.
c. Description of the patient's efforts to relieve the symptoms	None. She states that she has been wearing some concealer to "hide" the spots.
d. Patient's identity	Bailey Marshall
e. Patient's age, gender, height, and weight	18 years, female, 5 ft 5 in., 135 lb
f. Patient's occupation	College student who studies dance.
g. Patient's dietary habits	Eats a healthy breakfast and lunch; has a homecooked dinner most nights. On dance recital nights she usually eats fast food

Relevant Evaluation Criteria	Scenario/Model Outcome
	while traveling.
h. Patient's sleep habits	She gets about 8 hours of sleep most evenings.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	<i>Asthma</i> : albuterol inhaler 90 mcg; inhale 1–2 puffs every 4–6 hours as needed
j. Allergies	None
k. History of other adverse reactions to medications	None
l. Other (describe) -----	History of mild acne that responded to self-treatment with salicylic acid face wash
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s) (Table 38–2).	The current presentation of papule formation accompanied by few pustules is consistent with mild acne, likely stress-induced from her dance performances.
3. Identify exclusions for self-treatment (Figure 38–3).	If her acne worsens or begins to cause scarring
	If she is pregnant or plans to become pregnant soon
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer Ms. Marshall to an appropriate health care provider. (2) Recommend self-care with available nonprescription products and nondrug lifestyle modifications. (3) Recommend self-care until the patient can see her

Relevant Evaluation Criteria	Scenario/Model Outcome
	regular health care provider. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Recommend that Ms. Marshall use an over-the-counter acne treatment product and implement nondrug measures to minimize/control her acne.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Using an over-the-counter formulation of a benzoyl peroxide gel and following some simple steps to modify your lifestyle would be a great option for you." See the box "Patient Education for Acne" for additional information.
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Benzoyl peroxide is an effective over-the-counter acne treatment. You likely have a mild form of acne, and this medication should help alleviate any breakouts and help prevent them from occurring. Although this medication should help, it is important that you consider that the acne may be linked to your stress. Engaging in stress management techniques also may be beneficial."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
a. Appropriate dose and frequency of administration	"Start by applying a thin layer of the gel once daily to a few affected areas for 2–3 days. If you do not experience significant skin irritation, the product can be applied in a thin layer once daily to affected areas for 1–2 weeks. If this regimen does not result in significant skin irritation, you can slowly increase the

Relevant Evaluation Criteria	Scenario/Model Outcome
	applications to 2–3 times daily thereafter as tolerated.” See the box “Patient Education for Acne” for additional information.
b. Maximum number of days the therapy should be employed	“If skin irritation develops with use of the product, it should be discontinued immediately. Otherwise, there is no maximum number of days for use of this medication. Continued and consistent use is required for full effectiveness.” See the box “Patient Education for Acne” for additional information.
c. Product administration procedures	“Apply a thin layer of the gel topically. Avoid touching hair or clothing as this product may cause bleaching. Wash and dry hands before and after applying. Avoid all mucous membranes while applying (eyes, nose, mouth). Wear a protective sunscreen if you will be spending a significant time in the sun because the medication increases your risk for sunburn.” See the box “Patient Education for Acne” for additional information.
d. Expected time to onset of relief	“You may see improvement in your skin within a few days of using the gel; however, it can take many weeks (ranging anywhere from 3 to 6) to see the full effect.”
e. Degree of relief that can be reasonably expected	“You should notice fewer breakouts with diminished redness and yellow pimples. Even with lifestyle changes, it could take some time before improvement is seen.”
f. Most common adverse effects	“Common adverse effects that can occur with use of this gel are related to general skin irritation and include redness, burning, peeling, and itching.” See the box “Patient Education for Acne” for additional information.
g. Adverse effects that warrant medical intervention should they occur	Intolerable skin irritation. See the box “Patient Education for Acne” for additional information.
h. Patient options in the event that condition worsens or persists	“If you do not experience improvement in 6 weeks or if the acne worsens, you should consult your regular health care provider and consider other treatment alternatives.” See the box “Patient Education for Acne” for additional information.
i. Product storage requirements	“Store at room temperature, out of reach of children and pets.”

Relevant Evaluation Criteria	Scenario/Model Outcome
j. Specific nondrug measures	“Consider using an oil-free concealer to prevent oil buildup on the skin, which can worsen acne. Stress management techniques also may be beneficial to reduce your body’s acne response.” See the box “Patient Education for Acne” for additional information.
Solicit follow-up questions from the patient or caregiver.	“Would a salicylic acid wash work better? When I had acne problems before, I just used it and it helped.”
Answer the patient’s or caregiver’s questions.	“Topical washes and cleansers do not leave a lot of the active acne-fighting ingredient behind, oftentimes making them less effective treatment options. Using a wash instead of the benzoyl peroxide would not be as effective in clearing and preventing future breakouts. Using the products together could lead to extreme skin drying and peeling.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Ms. Marshall in 2 weeks to see if she has experienced any decrease in her acne and to check for toleration of the product recommended. Recommend that she contact her regular health care provider if her acne worsens or if she does not see improvement after 6 weeks of consistent treatment.

Case 38–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient’s symptoms and medical history,	

Relevant Evaluation Criteria	Scenario/Model Outcome
including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient, a young man with severe acne on cheeks and chin, presents to the pharmacy for self-care recommendations. The acne lesions are large and cystlike in form and appear inflamed. He complains of intense burning when he tries to “pop the zit,” as well as periodic itching. His symptoms began 2 weeks ago when the weather started to get very humid. The patient states that he has had acne since he was a teenager, but it recently has gotten worse. He reports running regularly during the summer in nature parks. He also spends a lot of time outside for his botany internship.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Patient states that his acne started worsening when he began to run outside every day. Patient claims some relief of pain and itching when he takes cool showers and stays out of the sun. Claritin D also has helped with the itching.
c. Description of the patient's efforts to relieve the symptoms	Patient has consistently used nonprescription benzoyl peroxide 10% gel and an acne facial wash containing salicylic acid for 6 weeks, with no significant improvement.
d. Patient's identity	Adam Adenola
e. Patient's age, gender, height, and weight	24 years, male, 5 ft 8 in., 150 lb
f. Patient's occupation	University graduate student
g. Patient's dietary habits	Patient follows a vegetarian diet.
h. Patient's sleep habits	Patient sleeps 4–10 hours a night, depending on his course work and internship schedule.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	<i>Seasonal allergies:</i> Claritin D (loratadine/pseudoephedrine) in the spring and fall. This medication has helped with the itching associated with the acne.

Relevant Evaluation Criteria	Scenario/Model Outcome
j. Allergies	Spring allergies, no known drug allergies
k. History of other adverse reactions to medications	None
l. Other (describe) _____	Patient has a history of mild acne, for which nonprescription products generally have been of benefit.
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s) (Table 38-2).	Patient is suffering from acne inflammation due to bacteria buildup with resulting formation of cystlike lesions.
3. Identify exclusions for self-treatment (Figure 38-3).	Severe skin symptoms, cyst formation; resistance to treatment with nonprescription products
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer the patient to an appropriate health care provider. (2) Recommend self-care with a nonprescription acne and nondrug measures. (3) Recommend self-care until Mr. Adenola can see an appropriate health care provider. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem,	Patient should be referred to an appropriate health care provider for further evaluation.

Relevant Evaluation Criteria	Scenario/Model Outcome
taking into account patient preferences.	
6. Describe the recommended therapeutic approach to the patient or caregiver.	"You should consult a knowledgeable health care provider for treatment of your acne lesions."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"General recommendations say that you should talk to an appropriate health care provider if you have seen no improvement of your skin after 6 weeks of self-treatment. Your acne is most likely caused from bacteria buildup in your skin, so you will need a prescription to obtain improvement."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	See the box "Patient Education for Acne."
Solicit follow-up questions from the patient or caregiver.	"Will popping the cysts myself help clear out the bacteria from my skin?"
Answer the patient's or caregiver's questions.	"Popping acne cysts is not advised because it can lead to scarring and formation of additional lesions, and it can make your skin susceptible to other infections."
Follow-up: Monitor and Evaluate	
9. Assess patient	Contact Mr. Adenola in 1-2 days to ensure that he has made an

Relevant Evaluation Criteria	Scenario/Model Outcome
outcome.	appointment for further medical care.

Patient Education for Acne

The goal of self-treatment is to control mild acne, thereby preventing more serious forms from developing. The condition usually can be managed with diligent and long-term treatment. The best approaches to controlling acne are use of cleansers and medications to keep the pores open and avoidance of factors and situations that worsen acne. For most patients, carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

Disease Information

- Acne is the result of several pathophysiologic changes that occur within the pilosebaceous unit located in the dermis, or middle layer of the skin.
- Acne may be controlled by using certain medications, but it is not curable, although resolution occasionally may occur over time.

Nondrug and Preventive Measures

- Cleanse skin thoroughly but gently twice daily to produce a mild drying effect, which loosens comedones for removal. Use a mild, oil-free cleanser and warm water.
- To prevent or minimize acne flares, consider using a skin toner to remove excess dirt and oil. Avoid or reduce exposure to environmental factors such as dirt, dust, petroleum products, cooking oils, or chemical irritants.
- To prevent friction or irritation that may cause acne flares, do not wear tight-fitting clothes, headbands, or helmets; avoid resting the

chin on the hand.

- To minimize acne related to cosmetic use, use noncomedogenic, oil-free makeup and frequently clean cosmetic brushes, if used.
- To prevent excessive hydration of the skin, which can cause acne flares, avoid environments with high humidity.
- Avoid stressful situations when possible and practice stress management techniques. Stress can worsen existing acne.
- Do not pick or squeeze pimples, which can further irritate skin and possibly lead to infection, worsening of acne, and scarring.
- Note that sexual activity plays no role in the occurrence or worsening of acne, although the onset of sexual activity and occurrence of acne may take place within the same time span.

Nonprescription Medications

- Most commonly available nonprescription products contain adapalene, benzoyl peroxide, salicylic acid, or sulfur, and these products come in a variety of formulations (e.g., cleansers, creams, gels, astringents).
- Benzoyl peroxide and adapalene are the most effective nonprescription medications for treating mild acne.

Adapalene

- Adapalene is believed to normalize the development of skin cells, resulting in decreased acne symptoms.
- Do not use adapalene if you have very sensitive skin or are sensitive to benzoyl peroxide.
- Because adapalene increases susceptibility to sunburn, avoid unnecessary sun exposure and use a broad-spectrum sunscreen with an SPF of 15 or higher when using this product.
- To avoid possible excessive irritation, avoid contact of adapalene with eyes, lips, mouth, and nose, as well as cuts, scrapes, and other abrasions.
- Use of other acne medications with adapalene may cause excessive dryness and peeling. Such combination therapy should be directed by a knowledgeable health care provider.

- Redness, itching, dryness, scaling, and burning are common adverse effects that tend to diminish after the first month of treatment.
- Acne may worsen temporarily after beginning treatment with adapalene.
- It will take 8–12 weeks of treatment with adapalene before noticeable clinical improvement is obtained.
- If acne lesions or symptoms worsen or improvement does not occur in 3 months with proper use of the agent, consult your primary care provider.
- If you experience allergic reactions, become pregnant, or are planning to become pregnant, discontinue use of adapalene and consult your primary care provider for other treatment options.

Benzoyl Peroxide

- Benzoyl peroxide inhibits the growth of *Cutibacterium acnes*, the bacterium involved in acne development; it also helps unclog pores by causing a mild peeling effect.
- Do not use benzoyl peroxide if you have very sensitive skin or have a recognized sensitivity to this agent.
- Because benzoyl peroxide increases susceptibility to sunburn, avoid unnecessary sun exposure and use a broad-spectrum sunscreen with an SPF of 15 or higher when using this product.
- To prevent possible excessive irritation, avoid contact of benzoyl peroxide with eyes, lips, mouth, and nose, as well as cuts, scrapes, and other abrasions. Avoid contact of benzoyl peroxide with hair and dyed fabrics, which may be bleached by this product.
- Skin irritation, characterized by redness, burning, itching, peeling, or possibly swelling, may occur with the recommended treatment regimen. Irritation may be reduced by using the product less frequently or in a lower concentration.
- Note that use of other acne medications with this product may cause excessive dryness and peeling. Do this only as directed by a knowledgeable health care provider.
- After the initial 1–2 weeks of treatment, applications can be increased up to 2–3 times per day over a period of 2–3 days, as

tolerated.

- Slight improvement may be noticed in as little as a few days, but maximum effectiveness may take up to 3–6 weeks of continued use.
- If treatment is tolerated but the problem persists, the benzoyl peroxide strength may be increased to 5% after 1 week and to 10% after 2 weeks, if necessary.
- Continue the treatment regimen even after lesions have cleared to prevent the formation of new ones.

Salicylic Acid

- Salicylic acid helps unclog pores by causing slight peeling.
- This agent is less effective than benzoyl peroxide and adapalene.
- Salicylic acid can be used 1–3 times daily as a cleanser or as a topical gel.
- Gel formulations should be applied only to the affected area.
- If excessive peeling occurs, limit use to once daily or every other day.
- Salicylic acid may cause sun sensitivity, so limit sun exposure and use a broad-spectrum sunscreen with an SPF of 15 or higher.
- Lack of response after 6 weeks is an indication of need for medical referral.

Sulfur

- Sulfur is believed to work by inhibiting the growth of *C. acnes*.
- This medication can be applied 1–3 times daily, but its use is limited by its chalky yellow color and characteristic unpleasant odor.
- Sulfur is not as effective as benzoyl peroxide or adapalene.
- Patients who are allergic to sulfa drugs should not use sulfur-containing acne products.

When to Seek Medical Attention

- If severe skin irritation or sensitivity develops, stop use of irritant and see an appropriate health care provider.
- If improvement has not occurred after 6 weeks of treatment with benzoyl peroxide or salicylic acid or 8–12 weeks of adapalene, seek

further medical evaluation.

- If you experience tightness in the throat, breathing problems, feeling faint, or swelling of the eyes, face, tongue, or lips with use of an acne product, seek emergency medical attention.

Key Points for Acne

- Acne is not a curable condition but may be controlled to improve cosmetic appearance and prevent progression to severe disease with resultant scarring.
- Adherence to treatment regimens is crucial in achieving a successful outcome.
- Minimizing environmental and physical factors that exacerbate acne can help limit the extent of the condition.
- Pharmacologic and nonpharmacologic therapies should be tailored to the individual patient.
- Medical referral should be considered for moderate to severe acne, presence of certain exacerbating factors (e.g., comedogenic drugs), possible rosacea, and acne resistant to self-treatment regimens.
- Proper counseling, including empathy and reassurance, will promote the patient's understanding that consistent treatment is needed for clinical improvement.

Chapter 39: Prevention of Sun-Induced Skin Disorders

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Exposure to ultraviolet radiation (UVR) is cumulative and can produce serious, long-term problems. Sunburn is the most common skin problem caused by excessive UVR exposure. However, other conditions that are either directly caused or exacerbated by UVR exposure include a group of photoaggravated skin disorders: premature aging, skin cancers, cataracts, and photodermatoses ([Table 39–1](#)).^{1,2}

Skin cancer is the most serious UVR-induced skin disorder. Cumulative sun exposure from childhood to adulthood may predispose a person to develop precancerous and cancerous skin conditions. Epidemiologic studies conducted since the 1950s demonstrate a strong relationship between chronic, excessive, and unprotected sun exposure and human skin cancer. Skin cancers such as basal cell, squamous cell, and melanoma are the most commonly diagnosed cancer malignancy in the United States. According to the most recent estimates, 3.5 million basal and squamous cell carcinomas were diagnosed in 2012. The American Cancer Society estimates approximately 96,500 cases of malignant melanoma were diagnosed in 2019.^{3–5} Avoiding excessive UVR exposure through the use of sunscreens and other measures will reduce the incidence of sun-induced skin disorders: sunburn, premature aging of the skin, photodermatoses, skin cancer, and other long-term dermatologic effects. Education about the safe and effective use of sunscreen and suntan products is a public health need. To perform this function, health care providers should be aware of the hazards of UVR and the criteria for selection and proper use of sunscreen products. Providers are encouraged to participate in efforts to educate the public about the morbidity and mortality associated with excessive UVR exposure.^{3–5}

Pathophysiology of Sun-Induced Skin Disorders

Ultraviolet Radiation

The UV spectrum is divided into 3 major bands: ultraviolet C (UVC), ultraviolet B (UVB), and ultraviolet A (UVA), all of which may cause or exacerbate sun-induced skin disorders. However, UVA and UVB primarily are responsible for photodamage because all UVC radiation is removed by the ozone layer.²

UVB is the most active UVR for producing erythema. UVB radiation that reaches the Earth is at its highest intensity from 10:00 AM to 4:00 PM. UVB once was considered the primary inducer of skin cancer; however, UVA is now known to also play a role in causing skin cancer. Both UVA and UVB primarily are responsible for photoaging effects.^{2,6} The only true therapeutic effect of UVB exposure is synthesis of vitamin D₃ in the skin. However, the availability of vitamin D-rich foods and supplements have eliminated the need for UVB exposure to increase vitamin D production. The American Academy of Dermatology position statement on vitamin D states that UVR exposure should not be used as a source of vitamin D because of the associated risks.⁷

Cloud cover, white or light-colored surfaces (e.g., snow, sand), and altitude all contribute to the amount of UVR exposure received. Severe sunburn may result even when an individual is sitting in the shade or cloud cover is present. Water reflects no more than 5% of UVR, allowing the remaining 95% to penetrate and burn the swimmer. Therefore, even if the swimmer is completely submerged, time in the water should be considered part of the total time spent in the sun. Dry clothes reflect almost all UVR. If light passes through dry clothing when held up to the sun, however, UVR also will penetrate the clothing. Tightly woven material offers the greatest protection. Wet clothes allow transmission of approximately 50% of UVR.^{2,8,9}

UVB is blocked by glass in automobiles. The laminated glass in automobile windshields filters most UVA. However, side windows are not made from laminated glass; therefore, a significant amount of UVA may pass through them to riders in the vehicle. Therefore, patients sensitive to UVA (e.g., those with photodermatoses, those taking photosensitizing drugs) should use an appropriate sunscreen even when driving with the windows closed.¹⁰

The Environmental Protection Agency has developed a UV index that uses a scale to rate the amount of skin-damaging UVR that reaches the earth's surface at any given time ([Table 39-2](#)). As the rating increases, the risk of

exposure increases. The noon UV index value typically is used; however, the UV index changes throughout the day. Factors that influence the UV index are time of day (UVR exposure is greater at midday than in the early morning or late afternoon); ozone (limited amounts of ozone increase the amount of UVR exposure); altitude; season (UVR exposure is greater in spring and summer); surface reflectivity; latitude (UVR exposure is increased in areas closer to the equator); and land cover (less tree cover increases UVR exposure).^{11,12}

TABLE 39–2 Global Solar UV Index

Rating Number	Interpretation of UVR Exposure Risk
1–2	Low
3–5	Moderate
6–7	High
8–10	Very high
11+	Extreme

Key: UV = Ultraviolet; UVR = ultraviolet radiation.

Source: [Reference 10](#).

Sunburn and Suntan

Sunburn and suntan present as reactions to UVR exposure. The degree to which a person will develop a sunburn or a tan depends on several factors, including type and amount of radiation received, thickness of the epidermis and stratum corneum, skin pigmentation, skin hydration, and distribution and concentration of peripheral blood vessels. Most UVR that strikes the skin is absorbed by the epidermis.

A sunburn is an acute reaction to excessive UVR exposure, resulting in inflammation of the exposed skin. Exposure to both UVA and UVB can result in sunburn. The cellular mechanism for this response is complex, involving skin cells and numerous inflammatory mediators. Erythema, swelling, and pain occur after UVR exposure, reaching a maximum response at 6–24 hours. A

sunburn usually resolves in 72 hours. However, the sunburn may occur sooner and last longer depending on the duration of exposure to UVR.^{6,13}

A suntan is produced when UVR stimulates the melanocytes in the skin layers to generate and redistribute melanin in the skin. UVA and UVB both contribute to the development of a suntan. Tanning may be described as immediate or delayed. *Immediate tanning*, caused by a redistribution of melanosomes, begins to be visible rapidly after exposure and may last for 3–4 days after UVR exposure. The darkening of pigment may not be visible on lighter skin types. *Delayed tanning* occurs because of the increase in number and activity of melanocytes after UVR exposure. Delayed tanning of the skin becomes visible 3–4 days after exposure to UVR and will last from 10 to 30 days depending on skin type and amount of UVR exposure. Delayed tanning serves as a protective mechanism for the skin to diffuse and absorb additional UVR. However, tanning does not protect an individual from developing skin cancer, photodermatoses, premature photoaging, or other UVR-related negative health risks. Tanning also does not protect against future sunburns.^{6,13}

Photodermatoses

The exact pathologic mechanism for the development of photodermatoses is unknown. UVB most often is responsible for these reactions; however, UVA and some visible light also may cause photodermatoses.

Photosensitivity encompasses two types of conditions: photoallergy and phototoxicity. *Drug photoallergy* involves an increased, chemically induced reactivity of the skin to UVR and/or visible light. UVR (primarily UVA) triggers an antigenic reaction in the skin. This reaction, which is not dose related, is usually seen after at least one prior exposure to the involved chemical agent or drug.

Similar to photoallergy, *phototoxicity* is an increased, chemically induced reactivity of the skin to UVR and/or visible light. However, phototoxicity is not immunologic. It often is seen on first exposure to a chemical agent or drug, is dose related, and usually exhibits no drug cross-sensitivity. Some drugs associated with phototoxicity are listed in [Table 39–3](#). This type of reaction is not limited to drugs: it also is associated with plants, cosmetics, and soaps.^{1,13}

TABLE 39–3 Selected Medications (by Drug Category) Associated With Photosensitivity Reactions

Anticancer Drugs

Dacarbazine

Daunorubicin

Fluorouracil

Methotrexate

Vinblastine

Anticonvulsants

Carbamazepine

Gabapentin

Lamotrigine

Phenytoin

Antidepressants

Bupropion

Selective serotonin reuptake inhibitors

Trazodone

Venlafaxine

Antihistamines

Cetirizine

Diphenhydramine

Antihypertensives

Angiotensin-converting enzyme inhibitors

Calcium channel blockers

Hydralazine

Labetalol
Methyldopa
Minoxidil
Sotalol
Anti-infectives
Azithromycin
Ceftazidime
Dapsone
Gentamicin
Griseofulvin
Itraconazole
Ketoconazole
Metronidazole
Pyrazinamide
Quinolones
Ritonavir
Saquinavir
Sulfonamides
Tetracyclines
Trimethoprim
Trovafloxacin
Zalcitabine
Antimalarials
Chloroquine
Quinine

Antipsychotics/Phenothiazines
Haloperidol
Olanzapine
Ziprasidone
Coal Tar and Derivatives
DHS Tar Gel Shampoo
Ionil T Plus Shampoo
Neutrogena T/Derm Body Oil
Neutrogena T/Gel Extra Strength
Diuretics
Acetazolamide
Amiloride
Furosemide
Metolazone
Triamterene
Thiazide diuretics
Nonsteroidal Anti-inflammatory Drugs
Celecoxib
Ibuprofen
Indomethacin
Methoxsalen
Naproxen
Sunscreens
Aminobenzoic acid
Aminobenzoic acid derivatives

Benzophenones
Cinnamates
Homosalate
Menthyl anthranilate
Oxybenzone
Miscellaneous
Amiodarone (antiarrhythmic)
Benzoyl peroxide
Gold salts (antiarthritic)
Isotretinoin (antiacne)
Quinidine sulfate (antiarrhythmic)
Retinoids
Statins

Source: [References 1, 6, 13](#), and Stein KR, Scheinfeld NS. Drug-induced photoallergic and phototoxic reactions. *Expert Opin Drug Saf.* 2007;6(4):431–443.

Skin Cancer

Melanoma causes the majority of deaths due to skin cancers. However, the majority of skin cancers are nonmelanoma skin cancers (NMSCs). These cancers commonly occur on sun-exposed areas of the body (face, head, neck, and backs of the hands). The two most common types of NMSC are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). BCC often is an aggressive, invasive disorder of the epidermis and dermis that can cause serious damage to the skin and underlying tissue; however, it rarely metastasizes. SCC found in epithelial keratinocytes grows very slowly and has only an approximately 4% annual incidence of metastasis.

The pathophysiology of melanoma differs from that of the NMSCs. Although most melanomas arise from normal skin, about 30% involve existing nevi

(moles).

Some of the risk factors for skin cancer include a family or personal history of melanoma; sun sensitivity (e.g., difficulty tanning, burning easily); large numbers of atypical nevi; a previous history of SCC or BCC; tanning bed use; and a history of excessive sun exposure and sunburns. Regardless of risk factors, skin cancer may develop in all individuals with increased exposure to UVR. A growing amount of evidence supports the supposition that sun exposure plays a role in the development of all types of skin cancers.^{5,6,13-17}

Clinical Presentation of Sun-Induced Skin Disorders

Sunburn

Sunburn usually is seen as a superficial burn with a reaction that ranges from mild erythema to tenderness, pain, and edema (see [Color Plates](#), photograph 28). Severe reactions to excessive UVR exposure can sometimes produce burns that range in severity from superficial partial thickness to full thickness, with the development of *vesicles* (blisters) or *bullae* (many large blisters) as well as fever, chills, weakness, and shock. Shock caused by heat prostration or hyperpyrexia can lead to death.^{6,13} (See [Chapter 41](#) for treatment of sunburn.)

Drug Photosensitivity

Drug photoallergy presents similar to allergic contact dermatitis (e.g., poison ivy) and is characterized by pruritus with erythematous papules, vesicles, bullae, and/or urticaria (see [Color Plates](#), photograph 29). *Phototoxicity* is most likely to appear as an exaggerated sunburn with pruritis,^{1,13} but urticaria also may occur (see [Color Plates](#), photograph 30).

Photodermatoses

Each photodermatosis has a unique morphology. *Polymorphous light eruption* alone can have multiple morphologic presentations of pruritus as papules, vesicles, plaques, and/or urticaria.¹

Premature Aging

Premature aging is characterized by wrinkling and yellowing of the skin. Conclusive evidence reveals that prolonged exposure to UVR results in *elastosis* (degeneration of the skin caused by a breakdown of the skin's elastic fibers). Pronounced drying, thickening, and wrinkling of the skin also may result. Other physical changes include cracking, *telangiectasia* (spider vessels), *solar keratoses* (growths), and *ecchymoses* (subcutaneous hemorrhagic lesions).^{5,6,13–16} (See [Chapter 40](#) for measures to reverse photoaging.)

Skin Cancer

BCC is a translucent nodule with a smooth surface. It usually is firm to the touch and may be ulcerated or crusted. *BCC* generally is found as an isolated lesion on the nose or other parts of the face, although multiple lesions are sometimes found. Conversely, *SCC*, is a slow-growing, isolated papule or plaque on sun-exposed areas of the body.^{6,13}

Self-examination for melanoma uses four factors (A-B-C-D-E) for evaluation: Asymmetric shape; Border irregularity or poorly defined border; Color variation within the same mole or a change in color; Diameter larger than 6 mm; and an Evolving or a changing mole. A mole with these characteristics and any new growth or change in appearance of the skin (including the lips) should be evaluated by a dermatologist.^{17,18}

Prevention of Sun-Induced Skin Disorders

The short-term goals in preventing sun-induced skin disorders are relatively simple: avoid or minimize sunburn, photosensitivity reactions, and photodermatoses induced or exacerbated by UVR. The expected long-term outcomes are prevention of skin cancer and avoidance of premature aging of the skin.

UVR-induced skin disorders can be prevented by minimizing exposure to UVR and by using sunscreen agents. The sunscreen product selected and the degree of protection will vary, depending on the patient's intended use for the product and the conditions under which the product will be used ([Figure 39–1](#)).

FIGURE 39–1 Self-care for sun protection. Key: CAM = Complementary and alternative medicine; HCP = health care provider; SPF = sun protection factor. Source: References 1, 2, 5, 14, 15, 20, 21, and 24.

As the risk a patient has of developing a UVR-induced skin disorder increases, the need to avoid sun exposure increases accordingly. Providers can assist the patient in striking a balance between completely avoiding sun exposure, wearing protective clothing, and using sunscreen products. With regard to preventing sunburn, the patient's natural skin type will be the primary factor in determining the appropriate sun protection factor (SPF) of the sunscreen product. The lightness of a patient's natural skin and the speed at which the patient develops a burn determine the SPF required for the sunscreen product to prevent sunburn. However, all skin colors, including darker skin, can suffer UVR damage, so patients of all skin types should be counseled about protection from UVR.⁵

Avoidance of Sun Exposure

Complete avoidance of UVR often is the best approach for patients who have the physical characteristics or history listed in [Table 39–4](#) or who suffer from a UVR-induced skin disorder. People who refuse to stay indoors or who must be outdoors for extended periods should wear protective clothing. (e.g., a hat with a 4-inch brim, long pants, a long-sleeved shirt or special sun protective clothing embedded with agents that absorb UVR). Many clothing items now list an *ultraviolet protection factor* (UPF) rating on their label, which identifies how much UVR the clothing can filter out. Clothing items that are darker in color, have a tighter weave, or contain a UVR-absorbing agent tend to block out more UVR. When the patient is unwilling or unable to avoid the sun or to wear protective clothing, the next best choice is to use a sunscreen product.⁵

TABLE 39–4 Patient Risk Factors for the Development of UVR-Induced Problems

- Fair skin that always burns and never tans
- A history of one or more serious or blistering sunburns
- Blonde or red hair
- Blue, green, or gray eyes
- A history of freckling
- A previous growth on the skin or lips caused by UV exposure

- The existence of a UV-induced disorder
- A family history of melanoma
- Current use of an immunosuppressive drug
- Current use of a photosensitizing drug
- Excessive lifetime exposure to UVR, including tanning beds and booths
- History of an autoimmune disease

Key: UV = Ultraviolet; UVR = ultraviolet radiation.

Source: [References 6](#) and [13](#).

UVR Protection

SPF

Purchasers of sunscreens usually are familiar with SPF, which is one parameter for determining a sunscreen's effectiveness for UV protection. Another parameter, minimal erythema dose (MED), is used to calculate a sunscreen's SPF. The *MED* is defined as the "minimum UVR dose that produces clearly margined erythema in the irradiated site, given as a single exposure."¹⁴ It is a dose of radiation, not a grade of erythema.

The SPF is derived by dividing the MED on protected skin by the MED on unprotected skin. For example, if a person requires 25 mJ/cm² of UVB radiation to experience 1 MED on unprotected skin and requires 250 mJ/cm² of radiation to produce 1 MED after applying a given sunscreen, the product would be given an SPF rating of 10. As the SPF increases, the agent's effectiveness in preventing sunburn increases. If 60 minutes of sun exposure usually is required for someone to experience a sunburn, a sunscreen with an SPF of 6 (reapplied in sufficient amounts at the recommended intervals) will allow that person to stay in the sun 6 times longer (or 6 hours) before experiencing the same degree of sunburn. The SPF is product specific because it is calculated on the basis of the final formulation of the product and cannot be determined on the basis of the active ingredient alone. A product with an SPF of 15 blocks 93% of UVB. Raising the SPF to 30 increases UVB protection to only 96.7%, and an SPF of 40 blocks 97.5%.¹⁴

New regulations for the testing and labeling of nonprescription sunscreen

products have been proposed to update the testing requirements for the safety and efficacy of sunscreen products. The SPF value for sunscreen products is determined by a standardized testing protocol. All products with an SPF of 15+ will be required to meet a minimum standard of UVA and UVB protection; these products will be considered “broad spectrum.” The proposed regulation also will require any approved sunscreen products to follow an updated defined labeling format. Only sunscreens with an SPF value of 15+ that are used as directed, along with other skin protection measures, will be able to claim a reduction in the risk of skin cancer and early skin aging. Sunscreens with an SPF value between 2 and 14, regardless of their UVA and/or UVB coverage, can claim only to help prevent sunburn and will not be labeled as “broad spectrum.” These products must also carry the following label warning: “Skin Cancer/Skin Aging Alert: Spending time in the sun increases your risk of skin cancer and early skin aging. This product has been shown only to help prevent sunburn, not skin cancer or early skin aging.”^{19,20}

A sunscreen’s efficacy also is related to its *substantivity*—that is, its ability to remain effective during prolonged exercising, sweating, and swimming. This property can be a function of the active sunscreen, the vehicle, or both. Generally speaking, products with cream-based (water-in-oil) vehicles appear more resistant to removal by water than those with alcohol bases. FDA regulations propose prohibiting “waterproof,” “sweatproof,” and “sunblock” claims on sunscreen products because these terms overstate effectiveness. Further, water-resistance claims on the front label must indicate whether the sunscreen remains effective for either 40 or 80 minutes during swimming or sweating. These times are based on the standard testing procedure. Products that are not water resistant must bear instructions for users to wear a water-resistant product while swimming or sweating.²⁰

FDA also is proposing to limit the maximum SPF value on sunscreen labels to 60+. Products with a tested SPF of 60–80 will be labeled as “60+.” Sunscreens that claim higher SPF values will have to go through a new drug application process.

The dosage forms proposed as safe and effective for use in sunscreen products are sprays, oils, lotions, creams, gels, butters, pastes, ointments, and sticks. Other application dosage forms (e.g., towelettes, wipes) have not been approved as safe and effective.²⁰

Types of Sunscreens

According to the therapeutic definitions, topical sunscreens can be divided into two major subgroups: chemical sunscreens and physical sunscreens. *Chemical sunscreens* absorb and thus block the transmission of UVR to the epidermis. An active ingredient absorbs at least 85% of the radiation in the UV at wavelengths from 290 to 320 nm, but the agent may or may not allow transmission of radiation to the skin at wavelengths longer than 320 nm. *Physical sunscreens* are generally opaque; instead of absorbing UVR, they reflect and scatter it. An active ingredient in opaque sunscreens reflects or scatters all light in the UV and visible spectrums at wavelengths from 290 to 777 nm. The sunscreen thereby minimizes suntan and sunburn.

The proposed rule updated data for marketed sunscreens. Twelve sunscreen agents currently found in nonprescription products have not been formally evaluated for efficacy and safety: cinoxate, dioxybenzone, ensulizole, homosalate, meradimate, octinoxate, octisalate, octocrylene, padimate O, sulisobenzene, oxybenzone, and avobenzone. Two sunscreens—zinc oxide and titanium dioxide in concentrations up to 25%—are considered Category I (generally recognized as safe and effective, or GRASE). Two sunscreen agents—aminobenzoic acid, or PABA, and trolamine salicylate—are considered to be Category II (not GRASE) due to safety concerns. The ruling states that the risks associated with aminobenzoic acid (skin reactions) and trolamine salicylate (bleeding risks and salicylate toxicity) outweigh the agents' benefits.^{19,20}

TABLE 39–5 Sunscreens Found in Nonprescription Products		
Sunscreen Agent	UV Spectrum Activity	FDA-Approved Maximum Concentration (%)
ABA and Derivatives		
Padimate O	UVB	Information not available at time of publication
Anthranilates		
Meradimate	UVA	Information not available at time of publication

Sunscreen Agent	UV Spectrum Activity	FDA-Approved Maximum Concentration (%)
Benzophenones		
Dioxybenzone	UVB, UVA	Information not available at time of publication
Oxybenzone	UVB, UVA	Information not available at time of publication
Sulisobenzone	UVB, UVA	Information not available at time of publication
Cinnamates		
Cinoxate	UVB	Information not available at time of publication
Octocrylene	UVB, UVA	Information not available at time of publication
Octinoxate	UVB	Information not available at time of publication
Dibenzoylmethane Derivatives		
Avobenzene	UVA	Information not available at time of publication
Salicylates		
Homosalate	UVB	Information not available at time of publication
Octisalate	UVB	Information not available at time of publication
Miscellaneous		
Ensulizole	UVB	Information not available at time of publication
Ecamsule (terephthalylidene dicamphor sulfonic acid)	UVB, UVA	2
Titanium dioxide ^a	290–770	25

Sunscreen Agent	UV Spectrum Activity	FDA-Approved Maximum Concentration (%)
Zinc oxide ^a	290–770	25

^a Agent scatters (rather than absorbs) radiation in the 290–770 nm wavelength.

Key: UV = Ultraviolet; UVA = ultraviolet A; UVB = ultraviolet B.

Source: [References 6, 13, 15, and 20](#).

Chemical Sunscreens

Aminobenzoic Acid and Derivatives

Padimate O is a derivative of aminobenzoic acid used in sunscreens for UVB protection.^{15,21}

Anthranilates

The anthranilates are ortho-aminobenzoic acid derivatives. Meradimate is a weak UV sunscreen with maximal absorbance in the UVA range. It usually is found in combination with other sunscreen agents to provide broader UV coverage.^{15,21}

Benzophenones

The benzophenone group comprises three agents: dioxybenzone, oxybenzone (benzophenone-3), and sulisobenzene (benzophenone-4). As a group, these agents primarily absorb UVB radiation, but they can offer some protection against UVA. Many sunscreen formulations now contain benzophenones because of their broad spectrum of action and less likelihood of causing allergic reactions seen in some of the other sunscreen classes. Oxybenzone, also found in some cosmetic formulations, is a significant sensitizing agent among sunscreens.^{15, 21,22}

Cinnamates

Cinnamates include cinoxate, octinoxate, and octocrylene. Inclusion of octocrylene in commercial sunscreen preparations has increased, possibly

because of its broader spectrum of absorbance and its effectiveness as a photostabilizer. *Photostabilizers* are compounds often used in sunscreens to prevent the sunscreen agent from losing effectiveness upon exposure to sunlight. Octocrylene can decrease the rate at which other sunscreens degrade upon sun exposure. It often is combined with other sunscreens to improve their stability.

Unfortunately, cinnamates do not adhere well to the skin and must rely on the vehicle in a given formulation for their substantivity.^{15,21,22}

Dibenzoylmethane Derivatives

Avobenzone (butyl methoxydibenzoylmethane, originally known as Parsol 1789) is a new sunscreen agent that is effective throughout the UVA spectrum. However, this agent does not provide total protection throughout the entire UVA spectrum, so reactions from photosensitive drugs and chemicals still could occur. Its role in sunscreen products is to increase UVA coverage. Avobenzone is easily degraded by exposure to sunlight; it is found in newer sunscreen products combined with octocrylene, salicylates, 4-methylbenzylidene camphor, and micronized zinc oxide and/or titanium dioxide to enhance stability of the product and to extend the product's spectrum of coverage through the UVA and UVB spectrum.^{15,21,22}

Salicylates

Salicylic acid derivatives are weak sunscreens and must be used in high concentrations. They do not adhere well to the skin and are removed easily by perspiration or swimming.^{15,21}

Other Chemical Sunscreens

Ensulizole does not fit into any of the preceding classes. It is a pure UVB, water-resistant, broad-spectrum sunscreen. Ecamsule often is combined with octocrylene to increase the latter's stability to light.^{15,21}

Physical Sunscreens

Physical sunscreens (zinc oxide and titanium dioxide) are considered broad-spectrum UV protectants. They are used most often on small and prominently exposed areas by patients who cannot limit or control their exposure to the

sun (e.g., lifeguards). Earlier formulations of these agents were opaque and had an undesirable sticky or gritty sensation. Current formulations contain micro- or nano-sized particles of the agent. These formulations are transparent, which improves their cosmetic appeal. Because titanium dioxide increases the effective SPF of a product and extends the spectrum of protection well into the UVA range, the number of commercial products containing this agent has increased.^{15,21}

Combination Products

FDA has not recommended limits on the number of sunscreen agents that may be used together. However, each sunscreen agent must contribute to the efficacy of a product and must not be included merely for marketing promotional purposes.²⁰

The proposed regulation does limit the use of combination sunscreen and insect repellent products. Safety concerns for these products include their appropriate use and enhanced systemic absorption. Thus, FDA does not consider these combination products to be safe and effective.²⁰

Dosage and Administration Guidelines

The two major causes of poor sun protection from sunscreen use are application of inadequate amounts and infrequent reapplication.

For maximum effectiveness, sunscreens must be applied liberally to all sun-exposed areas of the body and reapplied at least as often as the label recommends. FDA-recommended labeling states that sunscreens should be applied 15–30 minutes before UV exposure and at least every 2 hours thereafter. Reapplication after every episode of swimming, towel drying, or excessive sweating also is recommended.^{20,21}

The standard for application of sunscreens is 2 mg/cm² of body surface area.²⁰ This standard means that, for sufficient protection, the average adult in a bathing suit should apply 9 portions of sunscreen of approximately ½ teaspoon each, or approximately 4 and ½ teaspoons (22.5 mL) total. The sunscreen should be distributed as follows:

- Face and neck (including ears): ½ teaspoon
- Arms and shoulders: ½ teaspoon to each side of body

- Torso: ½ teaspoon each to front and back
- Legs and tops of feet: 1 teaspoon to each side of body

Because of the cost of sunscreen products and the need to apply them often and in sufficient amounts, users may apply substantially less sunscreen than is required to provide adequate protection. Exposure to UVR should be within the limits of the SPF value of the sunscreen for the individual using the sunscreen. A higher SPF may be needed for longer or more intense exposure to UVR. The final rule requires that the sunscreen label recommend the following with regard to sunscreen application: Regardless of the water resistance of the product, it should be applied 15 minutes before sun exposure. Non-water-resistant products should be reapplied at least every 2 hours. Water-resistant products should be reapplied every 2 hours, after 40 or 80 minutes of swimming or sweating (as designated on the label), and immediately after towel drying.^{20,21}

Safety Considerations

The development of a rash, vesicles, hives, or exaggerated sunburn after use of the sunscreen product most likely is a sign of either a photosensitivity or an allergic reaction.^{1,22} The patient should be referred for medical evaluation of the situation. The degree of the reaction will determine what type of medical intervention (if any) is necessary.

A study published in the *Journal of the American Medical Association* on May 6, 2019, found that significant systemic absorption in excess of the FDA-established safety threshold of a plasma concentration of 0.5 ng/mL occurred after application of four commercially available sunscreens: avobenzone, oxybenzone, octocrylene, and ecamsule. The sunscreens were applied in a variety of common dosage forms, including sprays, creams, and lotions.²³ A follow-up study published in 2020 reported similar results. This study measured systemic absorption of six sunscreens (avobenzone, oxybenzone, octocrylene, homosalate, octisalate, octinoxate) used 1–4 times daily and applied to 75% of the body at a concentration of 2 mg/cm² for 4 consecutive days. The sunscreen formulations included aerosol spray, nonaerosol spray, pump spray, and lotion. The authors found that, after a single application, the mean plasma concentration of all six products exceeded 0.5 ng/mL by day 1.²⁴ Data from these studies support the need for additional safety monitoring for sunscreen products.

Product Selection Guidelines

Two primary factors will determine the best product for a given patient: the intended use of the product and specific patient characteristics. The decision of which sunscreen product to use must be based on the information obtained from both categories.

Articles have highlighted the environmental effects of chemical sunscreens on coral reefs and other aquatic life. The state of Hawaii and the city of Key West, Florida, have enacted bans on sunscreen products containing oxybenzone and octinoxate. The U.S. Virgin Island also has banned these products and the product octocrylene. The non-nanotized forms of approved physical sunscreen products—zinc oxide and titanium dioxide—appear to be safer for aquatic life. Patients should avoid products with a particle size of less than 100 nanometers if they are concerned about effects on the environment.^{25,26}

Intended Use

Some patients may want to use sunscreens to prevent sunburn or the photoaging effects of UVR, or to protect themselves from skin cancer. Others may need protection from sun exposure because they are taking photosensitive drugs or they suffer from a photodermatosis.

The higher the SPF of the sunscreen product, the greater the protection it provides against sunburn and tanning. Studies have shown that sunscreens can protect against the long-term hazards of skin cancer.^{5,15} Considerable research currently is being conducted on all aspects of UVR and its effects. However, experts are debating whether low-SPF products protect individuals from UV skin damage or allow them to receive dangerously high levels of UVR over extended periods of time. Because of the known health hazards associated with UVR, sunscreen products of at least SPF 15 should be recommended to patients.²⁰ Generally, if a product is to be used to prevent skin cancer, to reduce the chance of a photosensitivity reaction, or to reduce the risk of triggering a skin disorder induced or aggravated by UVR, a broad-spectrum SPF value of 15+ is needed.^{1,5}

Patient Factors

For patients not concerned with photosensitivity or photodermatoses, product selection is much simpler. The following factors can serve as a guide in

selecting products with the appropriate properties for a patient's particular situation.

The most important factors in product selection are the individual's natural skin type and tanning history. An SPF product of 30+ should be used by people who burn easily and, at best, tan minimally. If the individual plans to swim, participate in vigorous activity (e.g., sand volleyball), or work outdoors, the sunscreen product must be able to adhere to the skin more substantially than if the individual just lies on the beach. The expected duration of the physical activity also can help determine which sunscreen to use. Water-resistant products usually are effective for at least 40 or 80 minutes when used during the previously described activities.²⁰

At least one-third of the current commercial products are labeled "noncomedogenic," "fragrance-free," and "hypoallergenic." Noncomedogenic products do not plug the pores and, therefore, do not exacerbate acne. This property is especially important for teenagers, who usually spend more time outdoors than other age groups and generally would prefer not to use comedogenic sunscreens. Many patients are sensitive to various ingredients (e.g., fragrances, emulsifiers, preservatives). These patients should try to choose fragrance-free formulations or those that are hypoallergenic. The prevalence of a true allergy to sunscreen products has been reported as low as 1% in North Americans. However, adverse reactions to sunscreens are more common. Patients may develop phototoxic or photoallergic reactions to any sunscreen or inactive ingredient in the product. Although it may not be possible to determine which specific ingredient a patient is sensitive to, patients who have a history of sensitivity to sunscreens would do well to use a fragrance-free, hypoallergenic product, and to try to avoid using a product containing a sunscreen with which they had a previous reaction.^{21,22}

Some patients have normally dry skin; sunbathing can further exacerbate this problem. These patients should avoid ethyl and isopropyl alcohols, which are included in a number of commercial sunscreen products and can further dry the skin.

Use in Special Populations

FDA requires that sunscreen products be labeled with the statement "children under 6 months of age: ask a doctor." Caregivers should be extremely wary regarding sun exposure in children, especially infants. The American Academy

of Pediatrics recommends that infants younger than 6 months be kept out of direct sunlight and that parents/caregivers can apply a small amount of sunscreen with an SPF of 15+ to small areas such as the face or back of the hands.^{27,28} Although the evidence is not yet conclusive, researchers and providers agree that use of an SPF-15 product starting after 6 months of age and continuing throughout an individual's lifetime can reduce the incidence of long-term skin damage related to UVR. A product with an SPF of 30+ may further reduce sunburn, premature skin aging, skin cancer, and other skin problems.^{2,5}

Given the new data on systemic absorption of some chemical sunscreens, pregnant or lactating women may want to discuss the use of sunscreens with their health care provider to determine the safest choice for them and their fetus or nursing child.^{23,24} They also may choose a physical sunscreen containing zinc oxide or titanium dioxide, both of which have been classified as safe and effective.²⁰

Assessment of Sun-Induced Skin Disorders

The approach to UVR-induced skin disorders differs from that used in most self-care situations. These disorders are addressed from a preventive, rather than a treatment, standpoint.

Consequently, assessment of the patient should focus on *the individual patient characteristics* and *intended use* of the product. Clinical providers' interventions with patients occur in two primary situations. The first situation occurs when a patient requests a recommendation for a sunscreen product to prevent a burn and/or to allow development of a tan. The second situation is initiated by the provider when a patient is placed on a drug that can produce a photosensitivity reaction. In this second scenario, no real patient assessment is needed because prevention of exposure to UVR is the standard approach. Cases 39–1 and 39–2 are examples of assessment of patients with sun-induced skin disorders.

Patient Counseling for Sun-Induced Skin Disorders

Health care providers can provide a great service by counseling patients about the suntanning process and about proper selection and use of sunscreens.

One simple way to find out whether a patient is using a sunscreen properly is to ask how long the product currently being used has lasted. When applied properly, according to the suggested dosing guidelines and in accordance with the appropriate substantivity of the product, a sunbather could easily use about 1 ounce every 80–90 minutes. This use would amount to several ounces a day and several product containers per week. Incredibly, many frequent sunbathers use only one container in an entire season. This diminished usage demonstrates the importance of individuals’ receiving adequate counseling to get the protection they desire. The box “Patient Education for Protection from Sun Exposure” lists specific information to provide patients.

Patients should also be advised to wear sunglasses to protect their eyes from sun-induced damage. The box “A Word About Sun-Induced Ocular Damage” describes the categories of available sunglasses and their UVR filtration properties.²⁹

Case 39–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient’s symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient describes a history of sunburns, especially since she began taking gabapentin for neuropathic pain.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient’s symptom(s)	Staying completely out of the sun has been the only thing she has found that keeps her from getting burned, but she enjoys being outside and is trying to increase her exercise by walking 1–2 miles each day.
c. Description of the patient’s efforts to relieve the symptoms	She rarely uses sunscreens. She typically forgets to apply it before she leaves the house for her walk.

Relevant Evaluation Criteria	Scenario/Model Outcome
d. Patient's identity	Danessa Sam
e. Patient's age, gender, height, and weight	60 years old, female, 5 ft 5 in., 165 lb
f. Patient's occupation	Elementary school teacher
g. Patient's dietary habits	n/a
h. Patient's sleep habits	n/a
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Metformin 1000 mg 1 tablet twice a day; lisinopril 10 mg 1 tablet daily; gabapentin 300 mg 1 capsule 3 times a day
j. Allergies	None
k. History of other adverse reactions to medications	She cannot recall any.
l. Other (describe) _____	n/a
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	The patient is in need of sun protection to prevent sunburns and skin damage.
3. Identify exclusions for sun exposure (Figure 39-1).	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Use a nonprescription sunscreen product daily 15-30 minutes prior to the outdoor walk. (2) Avoid sun exposure by staying in the shade or indoors. (3) Take no action.
Plan	

Relevant Evaluation Criteria	Scenario/Model Outcome
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Regularly using a sunscreen product while outdoors will allow the patient to enjoy the desired outdoor activities while minimizing the risk of sun-induced skin disorders.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Use a sunscreen product with an SPF of 15 or higher that provides protection against UVA and UVB. A water-resistant product will be a better choice if you tend to sweat during the walks. Apply the product liberally to all sun-exposed areas of the body."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Correct use of a sunscreen product will allow you to enjoy time outdoors without getting a sunburn. A broad-spectrum sunscreen that provides both UVA and UVB coverage is preferred. Additionally, using a sunscreen such as ecamsule, which is water-resistant, may be preferred during periods of physical activity.
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	"Apply the sunscreen product every day 15 or 30 minutes prior to going out into the sun. If you are sweating, reapply the sunscreen at least every 2 hours as directed on the product label. If you are in the water, reapply every 40 or 80 minutes. You will need to apply the sunscreen as follows: • Face and neck (including ears): ½ teaspoon. • Arms and shoulders: ½ teaspoon to each side of body. • Torso: ½ teaspoon each to front and back. • Legs and tops of feet: 1 teaspoon to each side of body."
Solicit follow-up questions from the patient or caregiver.	"What should I do if I have a reaction to the sunscreen?"
Answer the patient's or caregiver's questions.	"If you develop a rash or other skin reaction to the sunscreen, stop using it and see your health care provider."
Follow-up: Monitor and Evaluate	

Relevant Evaluation Criteria	Scenario/Model Outcome
9. Assess patient outcome.	n/a

Key: n/a = Not applicable; SPF = sun protection factor; UVA = ultraviolet A; UVB = ultraviolet B.

Case 39–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The mother of a 3-month-old infant would like to know what sunscreen is safe. She takes her children to the park each day and is worried her child will get a sunburn
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Children under 6 months of age are not included on the labeling for sunscreen products.
c. Description of the patient's efforts to relieve the symptoms	n/a
d. Patient's identity	Cassidy Jones
e. Patient's age, gender, height, and weight	3 months old, female, 13 lb

Relevant Evaluation Criteria	Scenario/Model Outcome
f. Patient's occupation	n/a
g. Patient's dietary habits	Child is consuming formula per normal expectations with no issues.
h. Patient's sleep habits	Child is sleeping and napping per normal expectations with no issues.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	No current medications
j. Allergies	Mother is not aware that child has any allergies.
k. History of other adverse reactions to medications	Mother is not aware that child has had any adverse reactions to any medications
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Patient in need of sun protection
3. Identify exclusions for sun exposure (Figure 39-1).	Child younger than 6 months of age
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Recommend avoidance of additional sun exposure. (2) Recommend use of a sunscreen product. (3) Refer child to her pediatrician for recommended measures.
Plan	
5. Select an optimal	Mother of a young child needing advice on sun protection for

Relevant Evaluation Criteria	Scenario/Model Outcome
therapeutic alternative to address the patient's problem, taking into account patient preferences.	her 3-month-old infant. However there is no recommended product for children younger than 6 months.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"You should contact your child's pediatrician for advice on what sunscreens may be safe to use on her. You can practice other sun-safety habits such as keeping her out of the sun by moving to a shaded area, or using an umbrella or a stroller with a shade cover. The American Academy of Pediatrics also recommends dressing young children in lightweight clothing that covers their arms and legs, and putting a brimmed hat on them to provide protection from the sun."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"There aren't good safety data for use of sunscreen products in very young children, so avoidance of sun exposure is the best choice."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	See criterion 6.
Solicit follow-up questions from the patient or caregiver.	"Would it be okay to use just a small amount of sunscreen on her arms and legs?"
Answer the patient's or caregiver's questions.	"The safest recommendation is to eliminate sun exposure as much as possible and to talk with your child's health care provider."
Follow-up: Monitor and Evaluate	

Relevant Evaluation Criteria	Scenario/Model Outcome
9. Assess patient outcome.	n/a

Key: n/a = Not applicable.

Patient Education for Protection From Sun Exposure

The objectives of self-treatment depend on a patient's specific goal and health status. Protection from sun exposure can prevent sunburn or tanning, photosensitivity reactions in susceptible persons, or exacerbation of sun-induced photodermatoses. The primary long-term benefits are to prevent skin cancer and premature aging of the skin. For most patients, carefully following product instructions and the self-care measures listed here will help ensure optimal outcomes.

Avoiding/Minimizing Sun Exposure

- Avoid exposure to the sun and other sources of UVR, such as tanning beds/booths and sunlamps.
- The sun's rays are the most direct and damaging between 10:00 AM and 4:00 PM. Avoid sun exposure as much as possible during this time of day.
- Sunburn can occur on a cloudy or overcast day; 70%–90% of UVR penetrates clouds.
- Wear protective clothing (e.g., long pants, a long-sleeved shirt, and a hat with a brim). Tightly woven fabrics that do not allow light to pass through will provide the most protection.
- Use a beach umbrella or other protection to reduce UVR.
- Water and wet clothing allow significant transmission of UVR. Even

if the body is completely submerged, consider time in the water as part of the total time spent in the sun.

Use of Sunscreens

- An SPF of 15 or greater provides the greatest protection against sunburn and other UVB-induced skin problems.
- A broad-spectrum sunscreen product (e.g., avobenzone used in combination with padimate O and/or octocrylene, meradimate, titanium dioxide, one of the benzophenones) provides optimal protection against UVA and UVB sun exposure. This type of sunscreen is especially recommended if you have a sun-induced disorder, if you are taking photosensitizing drugs, or if you just want to reduce sun exposure as much as possible to prevent long-term effects.
- Apply first dose 15 minutes before exposure.
- Apply approximately 1 ounce of sunscreen over the exposed areas of the body, avoiding contact with the eyes. The sunscreen should be distributed as follows: $\frac{1}{2}$ teaspoon to the face and neck (including ears) area, $\frac{1}{2}$ teaspoon to each arm and shoulder, $\frac{1}{2}$ teaspoon to the front and back torso each, and 1 teaspoon to each side on the leg and top of the foot.
- Use the most substantive sunscreen available; water-resistant sunscreens are recommended if you will be in water or perspiring excessively.
- Reapply the sunscreen according to the label instructions, usually every 40 or 80 minutes for water-resistant sunscreens while swimming or sweating or after towel drying. Apply every 2 hours for non-water-resistant products or for water-resistant products if you are not swimming or sweating.
- Always check the expiration date on the sunscreen product. Sunscreens can lose their effectiveness.
- Higher altitudes and lower latitudes increase the amount of UVR to which an individual is exposed. Take proper precautions (e.g., use a sunscreen with a high SPF) to protect skin from UVR.
- Snow and sand reflect UVR. Take proper precautions to protect exposed skin (e.g., wear sunglasses, use high-SPF sunscreens).

- Keep sunscreen out of direct sun, which can reduce its potency.
- Continue to use a sunscreen as long you are taking a photosensitizing drug or exhibiting signs and symptoms of photodermatitis.
- Avoid sunscreens containing aminobenzoic acid derivatives, benzophenones, cinnamates, or meradimate if you have had a prior allergic reaction to a sunscreen product.
- Stop using the sunscreen if redness, itching, rash, or exaggerated sunburn occurs.

Key: SPF = Sun protection factor; UVA = ultraviolet A; UVB = ultraviolet B; UVR = ultraviolet radiation.

Evaluation of Patient Outcomes for Sun-Induced Skin Disorders

The short-term outcomes for sunscreen use are readily apparent. Twenty-four hours after use, no obvious sunburn, photosensitivity reaction, or eruption of photodermatosis will be present. This success indicates that the appropriate sunscreen agents and/or SPF were used. However, the long-term effects of UVR (e.g., skin cancer, premature aging of the skin) may take up to 20–30 years to become evident.

A Word about Sun-Induced Ocular Damage

Recent studies have demonstrated a relationship between both UVA and UVB in cataract formation. UVR has been shown to cause temporary injuries such as photokeratitis (a painful type of snow blindness associated with highly reflective surfaces). Another concern involves an increase in the incidence of uveal (iris plus ciliary body) melanoma. These concerns

are even more serious because of the erroneous belief that all sunglasses screen out UVR. In response, the Sunglass Association of America, working with FDA, has developed a voluntary labeling program. Abbreviated information concerning sunglasses' UVR-screening properties is directly attached to each pair, and brochures describing the appropriate use of each type of lens are available at outlets selling the sunglasses.²⁹

According to its UVR filtration properties, each pair of sunglasses is placed in one of the following three categories:

1. Cosmetic sunglasses block at least 70% UVB and 20% UVA. They are recommended for activities in nonharsh sunlight (e.g., shopping).
2. General-purpose sunglasses block at least 95% UVB and 60% UVA. With shades that range from medium to dark, they are recommended for most activities in sunny environments (e.g., boating, driving, flying, hiking).
3. Special-purpose sunglasses block at least 99% UVB and 60% UVA. They are recommended for activities in very bright environments (e.g., ski slopes, tropical beaches).

Key: FDA = Food and Drug Administration; UVA = ultraviolet A; UVB = ultraviolet B; UVR = ultraviolet radiation.

Key Points for Sun-Induced Skin Disorders

- UVR (UVA and UVB) triggers a variety of photodermatoses and causes sunburn, photosensitivity, skin cancer, premature aging of the skin, cataracts, and a variety of other medical problems.
- No form of UVR exposure is safe. Tanning and use of tanning beds can result in negative health effects.
- The effects of UVR are cumulative over an individual's lifetime.
- The best protection against UVR is avoidance. The next best approach is to wear a hat, long sleeves, pants, and UV-protective

sunglasses.

- Maximum protection is provided by using a broad-spectrum sunscreen of SPF 15+.
- Because broad-spectrum sunscreens provide added UVA protection, they are the best choice for preventing long-term effects of sun exposure, regardless of the patient's history.

Providers need to appreciate sunscreen products as therapeutic agents rather than cosmetics. Unfortunately, most patients have the latter view. This perception makes good patient counseling even more important. Reinforcing the need for proper selection of the appropriate sunscreen product and correct use of these products are key to educating the public and reducing the risks of UVR exposure.

Chapter 40: Skin Hyperpigmentation and Photoaging

Authors: Katherine S. O'Neal

Skin Hyperpigmentation

Hyperpigmentation, manifested as an area of skin darker than the surrounding skin, usually is a benign phenomenon that nevertheless is challenging to treat. The altered pigmentation may be perceived by the patient as a disfigurement, especially when it involves the face and neck and is in noticeable contrast to the surrounding normal skin color. Although products used to treat hyperpigmentation serve a cosmetic function, it is important to recognize that they are drugs, with characteristic potential for toxicity and adverse effects.¹

Pathophysiology of Skin Hyperpigmentation

Systemic illnesses as well as localized skin diseases may cause pigment cells to become overactive (resulting in skin darkening) or underactive (resulting in skin lightening).² Endocrine imbalances caused by Addison disease, Cushing disease, or hyperthyroidism and conditions such as pregnancy are capable of altering skin pigmentation. Metabolic disturbances affecting the liver, as well as certain nutritional deficiencies, can be associated with diffuse melanosis. Inflammatory dermatoses (e.g., contact dermatitis from poison ivy or acne lesions) or physical trauma to the skin (e.g., thermal burn) may cause prolonged postinflammatory hyperpigmentation. In addition, certain drugs ([Table 40–1](#)) have an affinity for melanin, forming complexes with the protein or inducing its accumulation to cause hyperpigmentation. Thus, skin hyperpigmentation resulting from these conditions may occur as a result of increased melanin and melanocyte production accompanied by increased activity of melanocytes or deposits of other darkening chemicals in the skin.^{3–5} *Melanocytes* (pigment cells) produce *melanosomes*, pigment granules that contain the protein melanin, a brown-black pigment. These cells can be viewed as tiny single-celled glands with long projections used to pass pigment particles into the keratinocytes, from which the particles migrate upward to the skin surface. The melanocyte is believed to provide protection from

ultraviolet radiation (UVR). Compared with “fair” skin, dark skin usually has a greater number of melanocytes, which explains why UVR-induced skin cancers of all types are less common in darker skinned persons.^{5,6} A higher melanocyte count also may be why people with dark hair or darker complexions (Fitzpatrick skin types IV–VI; [Table 40–2](#)) and persons of Hispanic, African American, African, or Asian ancestry have been found to be more susceptible to development of hyperpigmentation.⁷

TABLE 40–1 Medications That May Cause Hyperpigmentation

Amiodarone
Anticonvulsants (e.g., carbamazepine, phenobarbital, phenytoin)
Antimalarial agents (e.g., chloroquine, hydroxychloroquine)
Antineoplastic agents (e.g., busulfan, cyclophosphamide, daunorubicin, doxorubicin, fluorouracil)
Clofazimine
Heavy metals (e.g., arsenic, bismuth, gold compounds, mercury, silver)
Hormone replacement therapy
Minocycline
Oral contraceptives
Phenothiazines (e.g., chlorpromazine, clomipramine, imipramine, thioridazine)
Tricyclic antidepressants (e.g., amitriptyline, desipramine, imipramine)
Zidovudine

Source: Adapted from reference 2; and Law RM, Law DT. Dermatologic drug reactions and common skin conditions. In: DiPiro JT, Talbert RL, Yee GC, et al. eds. *Pharmacotherapy: A Pathophysiologic Approach*. 10th ed. New York, NY: McGraw-Hill Professional; 2017:e99.

TABLE 40–2 Fitzpatrick Skin Type Classification

Fitzpatrick Skin Type	Characteristics	Response to UV Light
I	Unexposed skin is bright white	Always burns
	Blue/green eyes typical	Peels
	Freckling frequent	Never tans
II	Unexposed skin is white	Burns easily
	Blue, hazel, or brown eyes	Peels
	Red, blonde, or brown hair	Tans minimally
	European/Scandinavian ancestry	
III	Unexposed skin is fair	Burns moderately
	Brown eyes	Average tanning ability
	Southern or Central European ancestry	
IV	Unexposed skin is light brown	Burns minimally
	Dark eyes	Tans easily
	Dark hair	
	Mediterranean, Asian, or Latino ancestry	
V	Unexposed skin is brown	Rarely burns
	Dark eyes	Tans easily
	Dark hair	
	East Indian, Native American, Latino, or African ancestry	
VI	Unexposed skin is black	Almost never burns
	Dark eyes	Tans readily
	Dark hair	

Fitzpatrick Skin Type	Characteristics	Response to UV Light
	African or Aboriginal ancestry	

Key: UV = Ultraviolet.

Source: Adapted from D’Orazio J, Jarrett S, Amaro-Ortiz A, Scott T. UV radiation and the skin. *Int J Mol Sci.* 2013;14(6): 12222–48. doi: 10.3390/ijms140612222.

The three types of hyperpigmentation that are amenable to self-treatment with topical nonprescription agents are ephelides, solar lentigines, and melasma.⁸ *Ephelides*, or *freckles*, are spots of uneven skin pigmentation that first appear in childhood, are exacerbated by the sun, and tend to fade with reduced sun exposure. *Solar* or “*senile*” *lentigines* (age spots or liver spots) appear on exposed skin surfaces, particularly in fair-skinned people, and are induced by UVR. *Melasma* (also called *chloasma*), a condition characterized by macular hyperpigmentation, usually on the face or neck, often is associated with pregnancy (the “mask of pregnancy”), the use of oral contraceptives, and sun exposure.

Clinical Presentation of Skin Hyperpigmentation

Melasma is a common form of hyperpigmentation that occurs more often in women than in men.² Depending on the underlying cause of hyperpigmentation, the clinical presentation can vary.^{1,4,9} Most notably, affected patients complain of persistent macular discoloration on the face or other sun-exposed areas. A centrofacial distribution (involving the forehead, cheeks, upper lip area, nose, and chin) is the most common pattern.^{1,2} The abnormal pigmentation typically consists of a more intense brown coloration than that of surrounding normal skin and may range in intensity from dark to faint. Clinical evidence of hyperpigmentation and photoaging (considered later in the chapter) and their response to treatment are not easily quantifiable using standard-light photography or by routine clinical evaluation. Fluorescence photography will detect subtle but significant decreases in diffuse and mottled hyperpigmentation after topical treatment, which helps to

clinically evaluate the skin changes and accurately assess the efficacy of topical products.¹⁰

Treatment of Skin Hyperpigmentation

Treatment Goals

The goal of treatment for skin hyperpigmentation is to diminish the degree of pigmentation of affected areas so that the skin tone of these areas is consistent with surrounding normal skin.

General Treatment Approach

The general approach to clinical management of hyperpigmentation focuses on the melanin production pathway and consists of two broad categories of interventions: (1) stopping the skin cells from overproducing melanin and inhibiting melanosome formation and melanin synthesis and (2) chemically or mechanically removing the top few layers of the skin's surface.^{1-3,5} Although good outcomes can be achieved by using either strategy, the best results are accomplished through a combination of the two.

Exfoliation used to treat hyperpigmentation involves physically buffing away surface-layer skin, or *microdermabrasion*, and applying chemical agents (e.g., alpha hydroxy acids [AHAs]). Chemical peels, used as adjunct therapy, may enhance the efficacy of topical products.^{1,4} Because of the risk of subsequent scarring with hyperpigmentation and other adverse events, microdermabrasion is not considered standard therapy. Abrading skin also may cause irritation and burning.

To prevent negation of the effects of treatment with either bleaching agents or pharmacologic therapy, it is essential to avoid even minimal exposure to UVR, as a lifelong commitment. On an ongoing basis, patients also must use broad-spectrum sunscreen agents with a sun protection factor (SPF) of at least 30 in combination with a physical blocker such as titanium dioxide or oxybenzone, and wear protective clothing and broad-brimmed hats, even after discontinuing the bleaching agent.^{9,-11} The algorithm in [Figure 40-1](#) outlines self-treatment for skin hyperpigmentation.^{1-9,11-13}

Pharmacologic Therapy

Management of hyperpigmentation as directed by the patient's primary care provider may begin with use of topical prescription agents composed of ingredients known to cause lightening of the skin primarily through inhibition of tyrosinase, the rate-limiting step in melanin biosynthesis. Such products include tretinoin (retinoic acid), azelaic acid, hydroquinone, and corticosteroids. The disorder also may be treated with laser therapy alone. Combination products or laser therapy sometimes may be effective for postinflammatory hyperpigmentation that is resistant to treatment with a single-agent nonprescription product.^{1,4,12}

A number of nonprescription agents have been used in skin-bleaching preparations. The standard agents have included hydroquinone 2%, ascorbic acid, arbutin, glycolic acid, niacinamide, and kojic acid. Newer products are being formulated with rucinol, tranexamic acid, and aloesin.^{4,12-16} Thus far, however, only preparations containing hydroquinone have been submitted to the U.S. Food and Drug Administration (FDA) Advisory Review Panel on Over-the-Counter Miscellaneous External Drug Products, and products containing this agent remain the most effective nonprescription skin-bleaching preparations available. AHAs, promoted as nonprescription agents for skin repair in management of photoaging, are used to treat both disorders. [Table 40-3](#) lists selected trade-name products.

TABLE 40-3 Selected Nonprescription Skin-Bleaching/Fading Products

Trade Name	Primary Ingredient(s)
Alpha Skincare Dual Action Skin Lightener	Hydroquinone 2%; glycolic acid 10%
MD Complete Dark Spot Corrector	Hydroquinone 2%
Clinicians Complex 6% Skin Bleaching Cream	Hydroquinone 2%; kojic acid 2%
DDF Fade Gel 4	Hydroquinone 2%; kojic acid; azelaic acid; salicylic acid
Bianco Rose	Hydroquinone 2%
La Roche-Posay Mela-D Pigment Control Concentrated Serum	Glycolic acid; lipo-hydroxy acid

Trade Name	Primary Ingredient(s)
QRx Labs Whitening Serum	Alpha arbutin 2%; kojic acid; licorice root
Murad Rapid Age Spot and Pigment Lightening Serum	Hydroquinone 2%; glycolic acid
Noreva IKLEN Depigmenting Serum	Rucinol
Philosophy Miracle Worker Dark Spot Corrector	Niacinamide
Shiseido White Lucent Intensive Spot Targeting Serum	Tranexamic acid
SkinCeuticals Pigment Regulator	Kojic acid 2%; emblica extract 2%; glycolic acid
Verso Skincare Dark Spot Fix	Retinol 8 with retinyl retinoate; niacinamide

Key: PHA = Polyhydroxy acid.

Hydroquinone

Skin-bleaching agents diminish hyperpigmentation by inhibiting melanin production within the skin.⁴ Hydroquinone (*p*-dihydroxybenzene), a skin-bleaching agent currently is available for self-treatment for skin hyperpigmentation.^{13,14,17} Hydroquinone is considered the mainstay as well as the gold standard of hyperpigmentation therapy.^{1,12,13,16} However, the safety of bleaching creams that contain hydroquinone continues to be reviewed in the literature.¹⁴ In 2006, FDA proposed withdrawing the tentative final monograph that approved skin-bleaching creams and suggested replacing to replace it with a final rule stating that all drug products (including hydroquinone) used in nonprescription products to lighten skin are no longer generally recognized as safe and effective owing to the potential increased risk for cancer and *ochronosis*, a bluish-black discoloration of skin that occurs where hydroquinone has been applied. Subsequently, However, in December 2009, FDA nominated hydroquinone to undergo additional studies to determine whether its use poses a risk to humans.^{1,18} The National Toxicology Program's review was unable to show carcinogenicity for hydroquinone in humans exposed to this agent.^{1,18,19} Additionally, a review of cases from the period 1966–2007 found *ochronosis* to be a rare event.¹

Hydroquinone and its derivatives act by reducing conversion of tyrosine to dopa and, subsequently, to melanin by inhibiting the enzyme tyrosinase.²⁰ Other possible mechanisms of action include destruction of the melanocyte or melanosomes.¹² Hydroquinone is available in a concentration of 2%.¹⁴ Combining hydroquinone with an exfoliant, such as topical glycolic acid (an AHA), topical tretinoin, or a corticosteroid has shown increased efficacy compared with hydroquinone monotherapy.^{12,17}

Hydroquinone 2% should be rubbed gently but thoroughly into affected areas twice daily. The agent should be applied to clean skin before application of moisturizers or other skin care products. It should not be applied to damaged skin or near the eyes. If no improvement is seen within 2 months, its use should be discontinued and a dermatologist or other primary care provider should be consulted.¹ Once the desired benefit is achieved, hydroquinone can be applied as often as needed in a once- or twice-daily regimen to maintain the lightened skin color. Because of the lack of safety data, hydroquinone is not recommended for children younger than 12 years. Contraindications to the use of hydroquinone include hypersensitivity to the product and appearance of ochronosis.¹ Although not directly contraindicated, hydroquinone should be used during pregnancy only if absolutely needed (i.e., in the original FDA pregnancy risk schedule, it was labeled a category C drug). It is not known if topical hydroquinone can cause fetal harm.^{16,18,19} Studies in rats have found inconclusive evidence, and the FDA ruling was that reproductive and teratogenic effects were not prominent.¹⁸ (See the Preface for a detailed explanation of the pregnancy data.)

Alternative Agents

Kojic Acid

Kojic acid, derived from certain species of fungus (e.g., *Acetobacter*, *Aspergillus*, *Penicillium*), can be found in cosmetic products promoted to treat hyperpigmentation in concentrations ranging from 1% to 4%.^{12,13} This ingredient usually is combined with AHAs, with or without hydroquinone. It is dosed and applied according to the product type (e.g., cream, soap, lotion, drops). Kojic acid works primarily by inhibiting the production of tyrosinase through chelation of its copper, which reduces melanin synthesis. It also, however, can help reduce melanin proliferation.^{12,13} Adverse effects associated with this product include contact dermatitis, stinging, and erythema.²¹ One

study comparing kojic acid 1% alone and in various combinations with hydroquinone 2% and betamethasone valerate 0.1% demonstrated better results with the combination regimen.¹³

Tranexamic Acid

Tranexamic acid (trans-4-aminomethylcyclohexanecarboxylic acid) is an agent that has been available for many years and used for melasma.^{1,4,12,16,22} It works by decreasing the generation of arachidonic acid, which decreases melanocyte-stimulating hormone and pigment production. Studies have evaluated topical, intravenous, and oral dosage forms.¹⁶ Topical use has been shown to provide improvement within 3 months.^{22,23} With oral use, improvement occurs within 8 weeks.^{4,12,16,22} The oral dose most commonly being studied is 250 mg twice daily or 750 mg/day, and the currently available topical preparation is applied twice daily.²⁴ The most common adverse effect of the topical form was irritation to the applied area.¹⁶ The adverse effects associated with the oral form have included mild gastrointestinal discomfort, hypomenorrhea, allergic skin rashes, and slight elevations in alanine transaminase.¹⁶ Currently, tranexamic acid can be found as an adjunct ingredient in some nonprescription serums.

Niacinamide

Niacinamide is a form of vitamin B₃ and acts as an anti-inflammatory agent. Although most pharmacologic treatments for hyperpigmentation disrupt tyrosinase activity, niacinamide instead works by preventing the transfer of melanin to keratinocytes, improving appearance of the skin not only in hyperpigmentation but also in photoaging (with decrease in associated redness and wrinkles).²⁵⁻²⁷ Topical niacinamide 2% has been shown to reduce hyperpigmentation after 4 weeks of treatment.²⁵ The most common adverse effects are redness, burning, and itching.²⁶ Niacinamide also has demonstrated efficacy when used topically in combination with other agents, such as desonide 0.05%, 2% tranexamic acid, or 2% *N*-acetyl glucosamine.²⁵⁻²⁷

Arbutin

Arbutin, a beta-d-glucopyranoside derivative of hydroquinone, is obtained from the extract of the bearberry plant.¹² It works by inhibiting tyrosinase and melanosome maturation.¹² A study using 3% arbutin with 4% nicotinamide, 1% bisabolol, and 0.05% retinaldehyde applied once daily to the affected areas

showed a beneficial effect in 30 days. Although the effect is dose dependent, higher concentrations have been found to induce hyperpigmentation.¹²

Product Selection Guidelines

Product selection should be based on a suitable dosage form (e.g., cream, lotion, gel) for the patient's skin type (dry, normal, oily) and anatomic site (face, neck). For example, an emollient cream-based product may be more suitable for dry skin, whereas a gel-based preparation may be preferable for an oily skin type.

Assessment of Skin Hyperpigmentation: A Case-Based Approach

Assessment should involve evaluating the affected areas to determine whether the skin changes are characteristic of freckles, melasma, or lentigines. The patient's medication history and health status are important factors in pinpointing possible causes of the hyperpigmentation.

Case 40–1 is an example of the assessment of a patient with skin hyperpigmentation.

Patient Counseling for Skin Hyperpigmentation

The types of hyperpigmentation that are amenable to self-treatment should be explained to the patient, and the importance of avoiding sun exposure during and after treatment should be emphasized. The product instructions should be reviewed with the patient to ensure a successful therapeutic outcome. The box "Patient Education for Skin Hyperpigmentation" lists specific information to provide in patient counseling. Of note, the Melasma Quality of Life Scale has shown that presence of melasma, of any degree, negatively affects quality of life, especially in terms of social life, recreation, and emotional well-being.²⁸ As the health care provider of first resort for many patients with such skin changes, the informed pharmacist can therefore play a significant role in optimizing the clinical outcome.

Evaluation of Patient Outcomes for Skin Hyperpigmentation

Follow-up evaluation of the patient’s progress should be performed after 2 months of therapy. If the pigmented area shows no improvement, referral to the patient’s primary care provider or a dermatologist is indicated. If the desired outcome has been achieved, the patient should continue applying the agent once or twice daily as needed, along with use of a sunscreen, to maintain lightening of the skin.

Algorithm: Skin Hyperpigmentation

FIGURE 40–1 Self-care for skin hyperpigmentation. Key: AHA = Alpha hydroxy acid; BSA = body surface area.

Case 40-1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient seeks the pharmacist's advice regarding darkening of areas of skin on her cheeks, which first appeared a year ago last summer and went away over the winter.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Patient states that after spending 1 day in the sun, she "can already tell it's coming back."
c. Description of the patient's efforts to relieve the symptoms	The patient tried topical moisturizing lotions and exfoliation creams.

Relevant Evaluation Criteria	Scenario/Model Outcome
d. Patient's identity	Jill Colter
e. Patient's age, gender, height, and weight	31 years, female, 5 ft 6 in., 160 lb
f. Patient's occupation	Full-time outpatient nurse
g. Patient's dietary habits	Patient eats a well-balanced diet. She drinks wine and beer occasionally.
h. Patient's sleep habits	She averages 5 hours of sleep per night during the week and 10 hours per night on the weekend.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	None
j. Allergies	None
k. History of other adverse reactions to medications	None
l. Other (describe) _____	n/a
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	The patient has hyperpigmentation of the centropacial region, which first appeared last summer.
3. Identify exclusions for self-treatment (Figure 40-1).	The patient has tried nonprescription moisturizing and exfoliation products.
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer Ms. Colter to her regular health care provider or dermatologist for further evaluation. (2) Try a skin-lightening agent. (3) Take no action.

Relevant Evaluation Criteria	Scenario/Model Outcome
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	The patient should try nonprescription products focused on skin-lightening or correcting dark spots.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Try a product containing hydroquinone 2% with or without added ingredients to increase the effects."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Moisturizers and exfoliation products that do not contain skin-lightening ingredients will not add much benefit."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	Apply daily sunscreen or moisturizer with an SPF of 30.
Solicit follow-up questions from the patient or caregiver.	"A friend told me about laser treatment. Do you think I should try this first?"
Answer the patient's or caregiver's questions.	"Hydroquinone is currently the nonprescription product with the most evidence supporting its effectiveness. You should try this for 2 months first."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Ms. Colter in 2-3 days to check for any adverse skin reactions. Then ask her to call you in 1 month to report her response to your recommendations.

Key: n/a = Not applicable; SPF = sun protection factor.

Patient Education for Skin Hyperpigmentation

The objective of self-treatment with skin-bleaching products is to diminish the degree of pigmentation in affected areas. For most patients, carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

Hydroquinone

- Use hydroquinone to lighten only limited areas of hyperpigmented skin that show brownish discoloration.
- Do not use these products on nevi (moles) or reddish or bluish areas, such as port wine discoloration.
- Time to initial response averages 6–8 weeks, but up to 3 months may be required before noticeable results are achieved.
- Test for possible irritant reactions to the product by applying it to a small test area and checking the area for redness, itching, or swelling after 24 hours.
- Do not apply the product near the eyes or to damaged skin.
- Apply a thin layer of the product to clean, dry skin in the affected area only. Rub product into the skin gently but thoroughly.
- If moisturizers or other topical agents are being used at the same time, apply the hydroquinone first.
- Before spending time outdoors, even briefly, apply an opaque sunblock or broad-spectrum sunscreen (see [Chapter 39](#)) to the affected area after applying the hydroquinone, unless the product already contains a sunscreen in the formulation.
- Once the desired lightening of skin is reached, apply the hydroquinone once or twice daily to prevent hyperpigmentation from recurring. Continue to protect the treated area from sun exposure.

When to Seek Medical Attention

Consult a primary care provider if

- No improvement is seen after 2 months of using hydroquinone.
- Skin pigmentation becomes darker during treatment with hydroquinone.

Photoaging

Photoaging, also referred to as premature skin aging or dermatoheliosis, is the pattern of characteristic skin changes associated with sun exposure. Persons with Fitzpatrick skin types I–III ([Table 40–2](#)) are more susceptible to photoaging. Most fair-skinned Americans will have some signs of photodamage by the age of 50 years. A variety of therapies to address photoaging are available, ranging from use of topical pharmacotherapeutic products, including certain cosmetics, to more invasive procedures such as botulinum toxin A injections, laser resurfacing, and skin-specific plastic surgery. Although some products are available by prescription only, many others are nonprescription, with AHAs being widely used to combat mild to moderate photodamage.²⁹

Pathophysiology of Photoaging

Aging skin results from a combination of intrinsic and extrinsic factors. Clinical and histologic changes that occur as intrinsic processes include genetically controlled skin and muscle changes, expression lines and sleep lines, and hormonal changes. Extrinsic factors are those associated with environmental influences such as UVR, smoking, wind, and chemical exposure.^{29–31} Medications known to induce photosensitivity can contribute to photoaging by making the skin sensitive to UVR (see [Chapter 39](#)).

Prematurely aged facial skin, with creases and wrinkles, dry texture, and blotchy hyperpigmentation, is largely attributed to cumulative UVR, or photoaging. Exposure to ultraviolet B (UVB) light (290–320 nm) is primarily responsible for photoaging, although the longer ultraviolet A (UVA) light

wavelengths (320–400 nm) contribute to damage as well.²⁹ The amount of UVA present in sunlight is 10 times that of UVB, which culminates in higher levels of exposure. UVA also can penetrate further to reach the dermal layer and can work synergistically with UVB to cause photodamage and skin cancers.

Microscopically, sun-damaged skin shows *dysplasia* (abnormal tissue development), atypical keratinocytes, and occasional cell necrosis. Irregularity of epidermal cell alignment also is common. Loss of collagen and elastin is seen deeper in the dermal layer.^{29–31}

Clinical Presentation of Photoaging

Clinical signs of photoaging include changes in color, surface texture, and functional capacity of the skin (Table 40–4). Photodamaged skin may have a sallow yellow color with discoloration and may show telangiectasias (visible distended capillaries). Textural changes include lack of characteristic smoothness, loss of subcutaneous tissue around the mouth, and epidermal thinning around the lips. As sebaceous glands hypertrophy, the skin begins to show coarse texture, with increased pore size. In addition, fine vellus hairs can develop into unwanted terminal hairs. Other manifestations of photoaging of the skin may include development of precancerous (actinic keratosis) and cancerous (basal cell, squamous cell, melanoma) tumors.^{29–31} Cosmetically, patients may notice freckling, discolorations, or *crow’s feet* (small parallel lines around the eyes). Postmenopausal skin is susceptible to reduced estrogen receptor stimulation of dermal metabolism and may undergo significant changes in collagen and moisture content. These changes lead to signs of skin aging, as evidenced by diminished elasticity and wrinkles.³¹

TABLE 40–4 Glogau Classification of Photoaging

Category	Characteristics
Type I: mild	No wrinkles, early photoaging, mild pigment changes
	20–30 years of age
Type II: moderate	Wrinkles in motion, early-moderate photoaging, keratoses palpable
	30–40 years of age

Category	Characteristics
Type III: advanced	Wrinkles at rest, advanced photoaging, obvious dyschromia and keratoses
	≥50 years of age
Type IV: severe	Only wrinkles, severe photoaging, yellow-gray skin
	≥60 years of age

Source: Glogau RG. Aesthetic and anatomic analysis of the aging skin. *Semin Cutan Med Surg.* 1996;15(3):134–138.

Treatment of Photoaging

Treatment Goals

The primary consideration in management is to prevent or minimize photodamage by using appropriate sun protection.³⁰ The goals of specific treatment for photoaging are (1) to reverse cumulative skin damage with efficacious prescription and nonprescription products and (2) to maintain the integrity of the skin and protect it from further extrinsic damage by making lifestyle changes and, most important, protecting the skin from further and prolonged sun exposure.

General Treatment Approach

The first step in preventing and treating photoaging of the skin is for the patient to commit to minimizing sun exposure by wearing sun-protective clothing, using large-brimmed hats, avoiding the sun during peak UVR times, and wearing sunscreen daily. Broad-spectrum sunscreens (UVA and UVB coverage) with an SPF of 30 can minimize further photodamage during any UVR exposure^{9,11,30} (see [Chapter 39](#)).

Proper cleansing of the skin removes bacteria, dirt, desquamated keratinocytes, cosmetics, sebum, and perspiration. However, excessive use of soap can lead to xerosis, eczematous dermatitis, and other pathologic skin conditions.³²

Pharmacologic Therapy

Various topical products are being used to treat aging skin. These products include vitamins, AHAs, and beta hydroxy acids (BHAs). Many pharmacotherapeutic ingredients in cosmetics, such as AHAs, function as active pharmaceuticals that are known to have a sustained effect on the skin.^{33,34} Of the vitamins, A, C, B₃, and E have the most evidence supporting their use in treatment and/or prevention of photoaging.^{14,33,34}

Hydroxy Acids

Current labeling on hydroxy acid (HA) cosmetic products includes recommendations for melasma, acne, collagen density, and fine wrinkling of photoaging.¹² The AHAs are used in various concentrations and in a wide array of available products. Most HA preparations are sold as cosmetics, and others are sold as pharmaceuticals through a health care clinic or other prescribing source.^{35–38} Nonpeeling AHA products range in concentration from 2% to 20%. As peeling agents (as used by estheticians or dermatologists), they are available in concentrations greater than 20%.³⁷

Many types of AHAs are available, with the most common being lactic and glycolic acids (Table 40–5). The Cosmetic Ingredient Review Expert Panel, the cosmetic industry’s self-regulatory body, concluded that use of AHAs in cosmetic products is safe if (1) concentrations are 10% or less, (2) the final pH is 3.5 or higher, and (3) the product is formulated with a sunscreen or includes directions to use a sunscreen.³⁹

TABLE 40–5 Selected Nonprescription Products for Photoaged Skin

Trade Name	Active Ingredient(s)
Glycolic Acid–Containing Products	
Aqua Glycolic Hand and Body Lotion	Glycolic acid 14%
Alpha Hydrox AHA Enhanced Anti-Wrinkle Crème	Glycolic acid 10%
Alpha Hydrox AHA Souffle	Glycolic acid 12%
DDF Glycolic Exfoliating Oil Control Gel	Glycolic acid 10%
DermaQuest Skin Therapy	Glycolic acid 5%; azelaic acid 2.5%; salicylic

Trade Name	Active Ingredient(s)
	acid 2%
Dr. Michelle Copeland AHA Face Cream	Glycolic acid 10%
M.D. Forte Facial Cleanser III	Glycolic acid 30%
Peter Thomas Roth Glycolic Acid Hydrating Gel	Glycolic acid 10%
Peter Thomas Roth AHA/BHA Cleaning Gel	Glycolic acid 10%; salicylic acid 2%
Reviva Labs Glycolic Acid Cream Exfoliation and Cell Renewal	Glycolic acid 10%
Retinol-Containing Products	
GlyMed Plus Retinol Restart Rejuvenation Serum	Retinol 5%
Paula's Choice Clinical 1% Retinol Treatment	Retinol 1%; vitamin C
Proactiv+ Skin Revitalizing Pads	Retinol
Exuviance Super Retinol Concentrate	Retinol
Salicylic Acid-Containing Products	
Paula's Choice Skin Perfecting 2% BHA Lotion Exfoliant	Salicylic acid 2%
Peter Thomas Roth Beta Hydroxy 2% Acne Wash	Salicylic acid 2%

Of the BHAs, salicylic acid is used widely, even as a chemical peel.³³⁻³⁸ Compared with AHA products, BHAs are more lipophilic and demonstrate keratolytic effects. Products containing BHAs as the active ingredients may be beneficial to acne-prone skin.

Polyhydroxy acids are the new generation of AHAs that appear to deliver results similar to those achievable with the alpha and beta hydroxy products, but with less irritation.³³

Used appropriately, HA products act as exfoliants by causing detachment of keratinocytes, resulting in a smoother, nonscaly skin surface with eventual

normalization of keratinization. The effect of the AHA product depends on its concentration and pH.^{17,33,36,37} The lower the pH, the more effective the product will be, and the higher the AHA concentration, the more deeply it will penetrate the stratum corneum. By improving skin elasticity, HAs have been shown to make skin more flexible and less vulnerable to cracking and flaking. Regular use has led to an increase in skin collagen and elastin and smoother skin texture, lessening of fine lines, and normalization of pigmentation.^{36–38}

Guidelines for treatment with HAs include identification of patient factors such as current and past medications, previous dermatologic and other procedures, and medical history, all of which may affect treatment outcome and influence patient expectations, which initially may be unrealistic.^{12,35} Care should be taken to apply HAs to dry skin, with an estimated wait time of 10–15 minutes after cleansing the face. It also is prudent to begin application gradually, starting every other night for approximately 1 week and then increasing the frequency, as tolerated, to a maximum of twice-daily application. HA products may make the skin more sensitive to sun exposure. Patients should be advised to use daily sunscreen or sunblock with an SPF of 30 or greater during use of AHAs and after discontinuation of the AHA regimen.^{33,35–38}

Common adverse effects of AHA and BHA products include mild transient stinging, burning, pruritus, skin lightening, and dryness. BHA products may be less irritating. Many of these effects can be ameliorated if products are used with caution and proper counseling. Patients also should be advised that other topically applied products, both medications and cosmetics, may contain active ingredients capable of exacerbating irritation (e.g., AHA, BHA, hydroquinone). Information regarding use during pregnancy and lactation is lacking; therefore, such use is not recommended.⁴⁰

Retinol and Retinaldehyde (Vitamin A Derivative)

Topical retinoids—tretinoin, isotretinoin, tazarotene, adapalene, retinol, and alitretinoin—constitute the mainstay of treatment for photoaging.³³ Retinol and its derivatives have been incorporated into many skin care formulations and are available in both prescription and nonprescription products. Retinoids increase collagen production and induce epidermal hyperplasia, which helps reduce the appearance of fine lines, improves skin texture, and corrects tone and skin elasticity. Retinol is very unstable and, with light exposure, easily degrades to biologically inactive forms.^{12,35} Thus, higher concentrations may be

needed for efficacy. Retinol is transformed into retinaldehyde and then into retinoic acid with a two-step enzymatic process that involves dehydrogenase in human keratinocytes. Topical retinaldehyde not only is well tolerated by human skin but also has been shown to have several effects identical to that of tretinoin. Common adverse effects of topical retinoids include scaling, redness, burning, and dermatitis. Retinoids may have to be used for at least 4 months before benefit can be seen. The use of vitamin A in women of childbearing age is controversial and should not be recommended in women who are pregnant or may become pregnant.³⁵

Ascorbic Acid (Vitamin C)

Ascorbic acid, or vitamin C, has antioxidant, anti-inflammatory, skin-lightening, and antihyaluronidase activity.^{14,33} Several studies have demonstrated reduced skin roughness and wrinkles with application of topical ascorbic acid 3%–5% for 12 weeks.^{14,33,35} Topical ascorbic acid also has been reported to have at least some photoprotective properties.³⁹ Of note, in the original FDA pregnancy risk schedule, this vitamin is labeled a category C drug.⁴¹ (See the Preface for a detailed explanation of the pregnancy data.)

Product Selection Guidelines

Skin type should determine the selection of product type. Creams are appropriate for drier skin types, lotions are best for combination or normal skin, and gels or solutions are useful for oilier skin. Use of products with higher concentrations and a lower pH may produce faster results. However, the patient should be forewarned that such products also may cause greater skin irritation.

Assessment of Photoaging: A Case-Based Approach

If careful inspection of the skin reveals signs of photoaging, the initial assessment should focus on the patient's history of UVR exposure, whether from sunlight or artificial sources (e.g., tanning beds). Knowledge of whether the patient's current occupational or recreational habits entail excessive UVR exposure is useful not only in determining the cause of the skin disorder but also in developing a treatment plan. It is important to assess for any diseases or current or past medication regimens that may predispose the skin to

premature photodamage or photosensitivity. The patient's health status, lifestyle practices, and daily skin maintenance regimen are other pertinent assessment criteria.

Case 40–2 is an example of assessment of a patient with photoaging.

Patient Counseling for Photoaging

Patient counseling should emphasize that premature wrinkling, creases, dry texture, and blotchy hyperpigmentation are not inevitable, and that proper protection from UVR can limit the effects of photoaging.¹¹ The health care provider should be proactive in identifying and recommending appropriate products for the patient's skin care needs. The box "Patient Education for Photoaging" lists specific information to provide in patient counseling.

Evaluation of Patient Outcomes for Photoaging

Patients using nonprescription skin care products to combat photoaging should be assisted to set reasonable aesthetic goals. Obviously, such preparations cannot "erase wrinkles." The health care provider should monitor the progress of the treatment and be aware of potential issues that warrant medical referral (e.g., reactive hyperpigmentation, bacterial or fungal infections, epidermal cysts, acneiform eruption, scarring).⁴²

Case 40-2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient is an older man seeking advice regarding the recent onset of wrinkles, dry skin, crow's feet around his eyes, and areas of darkened skin.

Relevant Evaluation Criteria	Scenario/Model Outcome
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	He had not noticed any specific skin changes until now. He recently retired and is working outdoors a lot more.
c. Description of the patient's efforts to relieve the symptoms	He uses daily moisturizer but wants to "have less-wrinkled skin," as well as to prevent more wrinkles and avoid any additional darkening of the skin.
d. Patient's identity	Greg Smith
e. Patient's age, gender, height, and weight	68 years, male, 5 ft 9 in., 195 lb
f. Patient's occupation	Retired
g. Patient's dietary habits	Patient eats fast food often. He drinks alcohol socially and quit smoking 3 years ago.
h. Patient's sleep habits	Normal sleep schedule; he averages 6 hours per night.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	<i>High blood pressure:</i> lisinopril 10 mg daily; hydrochlorothiazide 12.5 mg daily
j. Allergies	None
k. History of other adverse reactions to medications	None
l. Other (describe) _____	n/a
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	The patient has noticeable wrinkles, crow's feet, dry skin, and hyperpigmented areas on his face caused by photoaging.
3. Identify exclusions for self-treatment.	The patient has no exclusions for self-treatment.
4. Formulate a comprehensive list of therapeutic alternatives for	Options include

Relevant Evaluation Criteria	Scenario/Model Outcome
the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	(1) Refer Mr. Smith to his regular health care provider or a dermatologist for further evaluation. (2) Recommend a 2-month trial of a topical retinoid product with dark spot correction and use of daily sunscreen. (3) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	The patient would like to try a nonprescription product.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Apply the chosen product, such as Alpha SkinCare Dual Action Skin Lightener, to clean, dry skin once or twice a day in the morning and/or evening. Smooth the product over your face and neck, allowing the product to absorb completely. Then in the morning, also apply a broad-spectrum sunscreen with an SPF of at least 30. Use this sunscreen daily."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Seeing a dermatologist may not be necessary with proper use of this product. Wrinkles will not be completely removed because they are part of the natural aging process. The dark spots may lighten up a bit."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
a. Appropriate dose and	"Apply once or twice a day in the morning and/or

Relevant Evaluation Criteria	Scenario/Model Outcome
frequency of administration	evening. Smooth the product over your face and neck, allowing it to absorb completely. Apply a broad-spectrum sunscreen with an SPF of at least 30 after applying the product in the morning. Use this sunscreen daily."
b. Maximum number of days the therapy should be employed	"Improvement can be seen in as little as 4 weeks but may take as long as 6 months."
c. Product administration procedures	"The product should be applied after cleansing the face."
d. Expected time to onset of relief	"Improvement may be seen in as little as 4 weeks."
e. Degree of relief that can be reasonably expected	"Fine lines may be reduced, pore size may decrease, dark spots may lighten, and dryness should be less noticeable. The wrinkling, however, may not disappear completely."
f. Most common adverse effects	"Mild irritation may occur. In addition, the areas being treated may appear to be lighter than surrounding skin."
g. Adverse effects that warrant medical intervention should they occur	"If the treated areas of the skin become severely irritated or darken significantly, you should see your primary care provider or a dermatologist."
h. Patient options in the event that condition worsens or persists	"If no improvement is seen within 2 months, you should see your primary care provider or a dermatologist."
i. Product storage requirements	"When not in use, the product should be stored at normal room temperature and tightly closed, and out of the reach of children."
j. Specific nondrug measures	"This product may make the skin more sensitive to sun exposure. A sunscreen with an SPF of at least 30 should be applied daily while using this product and for up to a week afterward."
Solicit follow-up questions from the patient or caregiver.	(1) "May I use this product more than twice a day?" (2) "Should I always wear sunscreen or only when I am using this product?"
Answer the patient's or caregiver's questions.	(1) "No, this product should be used a maximum of twice daily."

Relevant Evaluation Criteria	Scenario/Model Outcome
	(2) "This product will increase the overall sensitivity of your skin to the sun. In addition, because you often are outside, you should use a moisturizer or sunblocker with an SPF of at least 30 every day and also wear a broad-brimmed hat for protection."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Ask Mr. Smith to call you in about 3–4 weeks to update you on his response to your recommendations. Or you could call him in 1 month to evaluate his response.

Key: n/a = Not applicable; SPF = sun protection factor.

Patient Education for Photoaging

The objectives of self-treatment are (1) to reverse skin damage by using available nonprescription products and (2) to prevent further damage by making lifestyle changes and protecting the skin from sun exposure. For most patients, carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

Alpha Hydroxy Acids

- Protect the skin from sun exposure by covering it with clothing. The U.S. Food and Drug Administration (FDA) recommends advising patients to wear long-sleeved clothing and hats with brim width of at least 4 inches. Patients also should commit to regular use of a sunblock or sunscreen product with an SPF of at least 30 for the duration of the alpha hydroxy acid (AHA) regimen and beyond, to prevent further damage.

- To prevent dry skin, cleanse the skin with a mild soap or a soap-free liquid cleanser. Do not cleanse skin more often than twice daily. Apply a pea-sized amount of an AHA product to clean, dry skin.
- To minimize transient mild tingling and stinging, wait 10–15 minutes after cleansing the face to apply an AHA product.
- Excessive skin dryness or irritation warrants decreased frequency of application.
- Note that AHA products contain an active ingredient and that the use of other products, including cosmetics, could result in skin irritation, including mild stinging, burning, or erythema.
- Do not apply the product too close to the eyes or mucous membranes.
- Begin applying this product once at bedtime every other day for approximately 1 week. Gradually increase application to twice a day.
- Use a daily moisturizer with sunscreen after applying the AHA product, to minimize dry skin and maintain the antiphotaging effect.
- Store this product in a cool dry place out of children's reach.
- Discontinue the AHA product if signs of severe irritation, such as redness or excessive dryness, appear or if a rash occurs.

Key Points for Skin Hyperpigmentation and Photoaging

- Photoaging and hyperpigmentation are cosmetically unacceptable skin conditions. Patients should be assisted to identify reasonable expectations with the use of nonprescription products, which should help to achieve even skin tone and to minimize appearance and occurrence of fine wrinkling.
- Hydroquinone is the only FDA-approved nonprescription skin-bleaching product. Patients should apply a 2% concentration to affected skin up to twice daily, as tolerated.

- Patients younger than 12 years, those with large areas of hyperpigmentation or disease- or drug-induced hyperpigmentation, and those with lesions showing changes in size, shape, or color should consult a dermatologist or their primary care provider.^{1,20}
- Patients should be referred to a dermatologist or their primary care provider if no improvement occurs within 2 months or if skin darkens during treatment for hyperpigmentation.¹
- Patients should avoid applying hydroquinone-containing products near the eye area or on damaged skin.
- Patients using HAs to reduce photoaging should be advised to apply the product to dry skin up to twice daily. Patients should be counseled that it may take up to 6 months to see the effect.
- Patients who use products to prevent photoaging or recurrence of hyperpigmentation should be instructed to protect the skin from daily sun exposure by using a sunscreen with an SPF of 30 to maintain results.

Chapter 41: Minor Burns, Wounds, and Sunburn

Authors: Nora Stelter

Thousands of people seek medical treatment for skin injuries each year. Annually, approximately 489,000 people with burn injuries and more than 1.2 million people with superficial skin injuries seek medical treatment at U.S. hospital emergency departments.¹ Sunburn at any age increases skin cancer risk, and every year, approximately one third of American adults experience sunburn. Sunburn is most prevalent in non-Hispanic white adults, although all ethnic groups experience preventable overexposure to ultraviolet radiation (UVR).² The most recent data for high school-aged children show that about five of every 10 high school boys and more than six of every 10 high school girls reported getting a sunburn in the previous year.³

Health care providers often provide guidance to patients seeking self-care recommendations for minor burns, sunburn, and wounds. Knowledge of common skin injuries, proper assessment of those injuries, and self-care recommendations are essential for health care providers who are likely to be consulted regarding treatment. Although healthy skin is well equipped for effective and efficient repair of minor acute skin injuries, providing patient education on appropriate self-care measures will help facilitate optimal healing, decrease the risk of complications, and minimize scar formation.

Pathophysiology of Minor Burns, Sunburn, and Wounds

Burns are wounds caused by exposure to UVR, or contact with thermal, electrical, or chemical sources. *Sunburn* is caused by overexposure to ultraviolet A (UVA) and ultraviolet B (UVB) rays from natural sunlight and from use of commercial tanning beds and tanning lamps (see [Color Plates](#), photograph 28). (See [Chapter 39](#) for a discussion of UVR bands.) *Thermal burns* result from skin contact with flames, scalding liquids, or hot objects (e.g., irons, hot pans, curling irons). *Electrical burns* occur when electricity flows through the body from an entry point to an exit point, and the heat of the electric

current damages the skin. *Chemical burns* occur secondary to exposure to corrosive or reactive chemicals that cause tissue damage. Some thermal burns and sunburns may be appropriate for self-treatment; however, all patients with electrical or chemical burns must be referred to a hospital emergency department for evaluation.

Wounds are injuries that cause a break in the skin. Minor wounds addressed in this chapter include abrasions and lacerations. *Abrasions* result from rubbing or friction applied to the epidermal layer of the skin, extending to the uppermost portion of the dermis. *Lacerations* (cuts and punctures) result from a sharp-edged object cutting through the various skin layers.⁴

Providers must understand the physiology of wound healing before they can recommend an appropriate course of action and provide patient counseling. Skin integrity depends on a delicate balance between structure and function. When a burn or wound disturbs this balance, prompt restoration is required to ensure that the body maintains homeostasis and that wounds heal properly.

The process of wound healing begins immediately after injury and consists of three overlapping phases: inflammatory, proliferative, and maturation (remodeling).⁵

The *inflammatory phase* is the body's immediate response to injury. This phase, which lasts approximately 3–4 days, is responsible for preparing the wound for subsequent tissue development and consists of two primary processes: hemostasis and inflammation. Hemostasis is initiated by the release of thromboplastin from the injured cells to form a clot. Clot formation is the main physiological process that stops bleeding so that tissue repair may begin. Later in the inflammatory phase, debris and bacteria are removed from the wound area, and collagen is formed to stimulate wound healing. Epithelial cells migrate to cover the wound bed and provide the initial layer (just one cell thick) of new skin that will cover the wound.⁵

In the next phase of healing, the *proliferative phase*, the wound is filled with new connective tissue and covered with new epithelium. This phase starts on day 3 or 4 and continues for approximately 3 weeks. The proliferative phase involves the formation of granulation tissue, which is a collection of new connective tissue (fibroblasts and newly synthesized collagen), new capillaries, and inflammatory cells.⁵

The final phase of healing, the *maturation* or *remodeling phase*, is the longest phase. It begins at approximately week 3, when the wound is completely closed by connective tissue and resurfaced by epithelial cells. This phase involves a continual process of collagen synthesis and breakdown, with replacement of earlier-constituted, weak collagen by high-tensile-strength collagen. This process peaks approximately 60 days after occurrence of the injury.⁵

Several local and systemic factors can affect how efficiently and to what extent a wound will heal. Providers who can recognize problems associated with these local and systemic factors can provide more effective wound care management instructions to aid in faster healing.

Local *factors* associated with delayed or otherwise poor healing include inadequate tissue perfusion and oxygenation; inadequate moisture; and the presence of foreign bodies (e.g., glass, dirt), necrotic tissue, or infection.⁶ Localized infection in the wound delays collagen synthesis and epithelialization, prolongs the inflammatory phase, and causes additional tissue destruction. Most minor wound infections are caused by bacteria, especially *Staphylococcus* and *Streptococcus*.⁷

Systemic factors that can impair the healing process are advanced age (>60 years); stress; inadequate nutrition; medical conditions such as diabetes and obesity; immunocompromised conditions such as cancer; alcoholism; smoking; and certain medications.⁶ Adequate nutrition provides the building blocks for wound repair, especially in chronic wounds. Protein, carbohydrates, vitamins, and trace elements are needed for collagen production and cellular energy. Medications that may impact wound healing include those that interfere with clot formation, platelet function, inflammatory responses, and cell proliferation.⁸ (See the section “Special Populations” for additional information.)

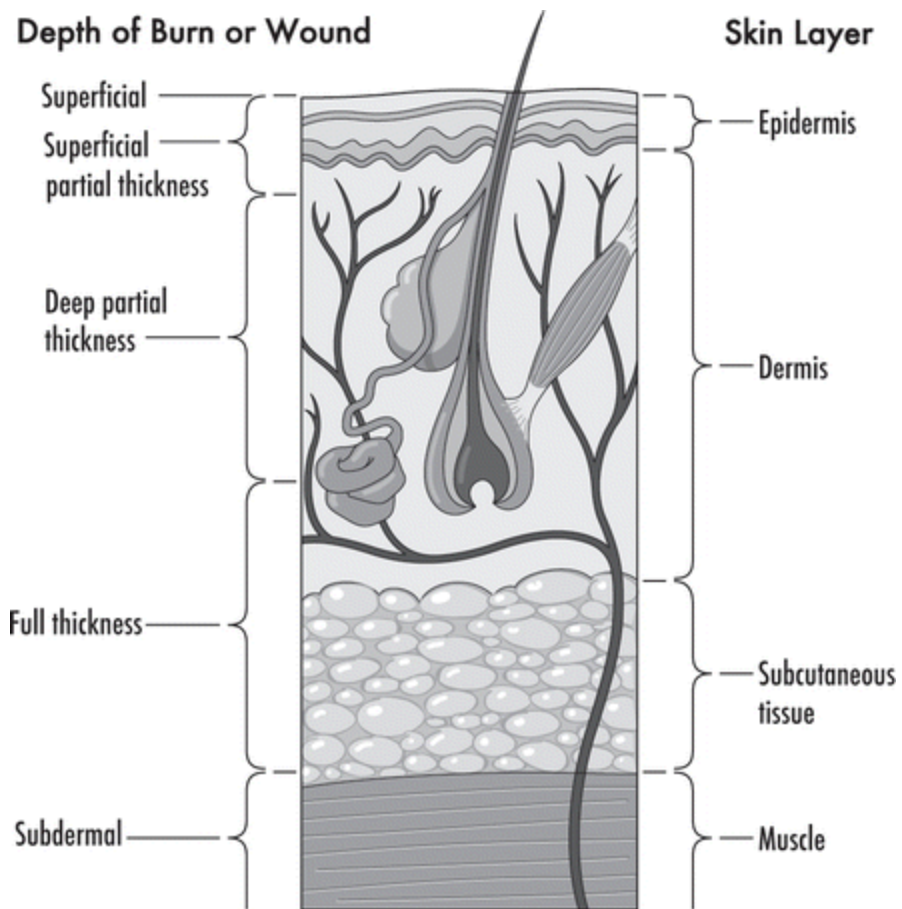
Clinical Presentation of Minor Burns, Sunburn, and Wounds

Minor burns, sunburn, and wounds are classified according to the cause of the injury; timing (whether the injury is acute or chronic); the depth of the injury

into the skin and underlying tissues; and the size of the injury.⁹ These factors determine whether the wound will heal with self-treatment or will require referral to a health care provider.

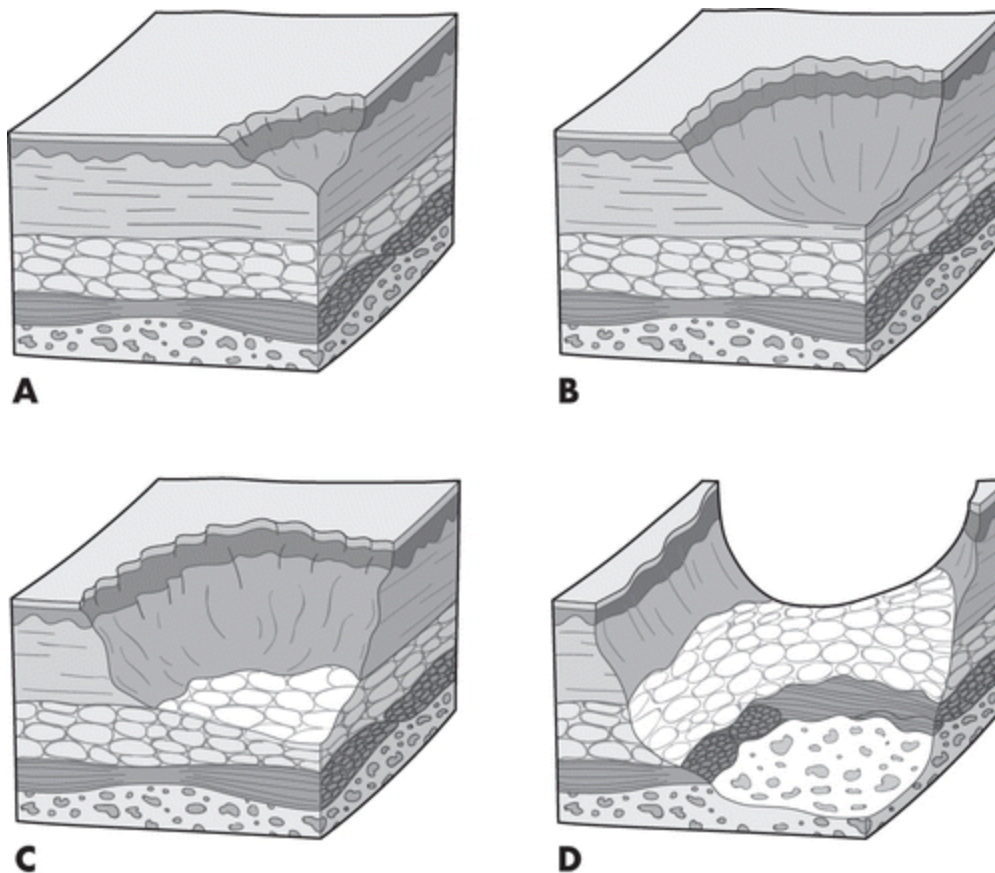
Skin injuries may be categorized as *acute* or *chronic* according to the rate of healing. *Acute wounds*, with proper care, tend to heal within 1 month in healthy adults. In contrast, any wound that does not heal properly through the normal stages of tissue repair and shows no progress toward healing in 30 days is considered a *chronic wound* and requires referral for more intensive medical care. Pressure ulcers (bed sores) and diabetic foot ulcers are examples of chronic wounds. This chapter discusses treatment of only minor burns, sunburn, and minor acute wounds.

Depth classification is divided into categories based on the increasing depth of the damage: superficial, superficial partial thickness, deep partial thickness, full thickness, and subdermal. [Figure 41-1](#) shows a cross-section of the anatomy of the skin and the depth of injury for burns or wounds of increasing severity. (See [Chapter 33](#) for further discussion of skin anatomy and physiology.) [Figure 41-2](#) illustrates the depth of burns and wounds whose depth exceeds that of a superficial skin injury.



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FIGURE 41-1 Cross section of skin showing depth of injury in burns or wounds of increasing severity.



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FIGURE 41-2 Depth of burns and wounds beyond a superficial skin injury. A: Superficial partial-thickness injury involves all of the epidermis and superficial dermis. **B:** Deep partial-thickness injury extends deeper into the dermis. **C:** Full-thickness skin injury extends beyond the dermis with damage to subcutaneous tissue. **D:** Subdermal skin injury extends beyond the subcutaneous layer and may damage muscle, bone, and interstitial tissue.

Superficial skin injuries involve only the epidermis, with no loss of any skin layers, and are characterized by reddened; nonblanching (does not become pale or white when pressure is applied to the skin); unbroken; and nonblistering skin that is painful to the touch. Minor sunburn is a superficial skin injury with erythema (superficial reddening of the skin) and slight dermal edema that results from increased blood flow to the affected skin. The erythema begins to develop approximately 3–5 hours after exposure, peaking between 12 and 24 hours.¹⁰ A majority of superficial injuries can be managed with self-care or through ambulatory care centers and will heal without

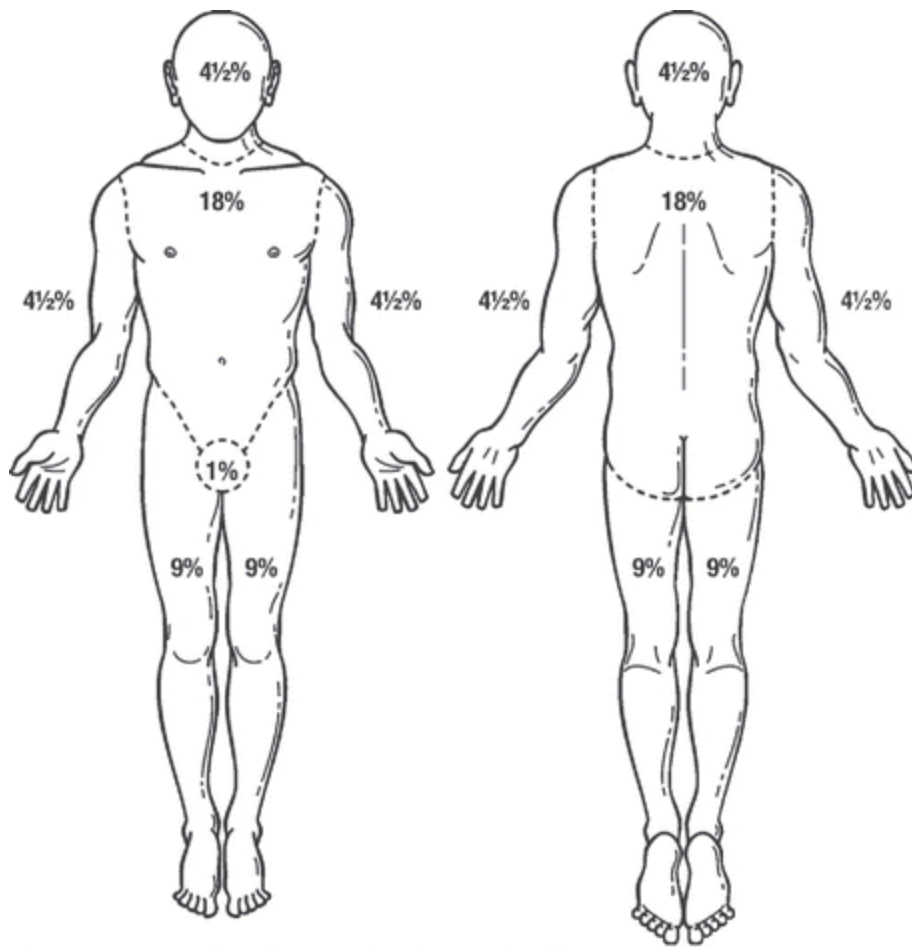
scarring within 3–7 days.^{11,12}

Superficial partial-thickness skin injuries involve all of the epidermis and the superficial dermis. Because the injury involves a break in the skin, drainage from the wound area may occur, in addition to pain, edema, and erythema. If pressure is applied to the skin, the area will blanch but have a rapid capillary refill upon release of pressure. Blistering may occur in some cases, such as in severe sunburn. Healing usually occurs with minimal scarring in 10–14 days.^{11,12} Minor superficial and superficial partial-thickness skin wounds may be managed with self-care if they meet criteria listed in [Figure 41-3](#).

Deep partial-thickness skin injuries extend deeper into the dermis and present with edema, less blanching, and typically no blisters. Pain sensation may be altered. Healing typically occurs in 2–4 weeks with scarring present. Patients with deep partial-thickness burns should be evaluated in a hospital emergency department.^{11,12}

Full-thickness skin injuries extend through the epidermis and dermis and into the subcutaneous tissue layer. *Subdermal skin injuries* extend beyond the damage to the subcutaneous tissue layer of muscle, bone, and interstitial tissue. Full-thickness and subdermal burns normally require hospitalization for treatment. Deep lacerations bleed profusely, and underlying tissue layers may be visible in the wound bed.^{11,12} Patients suffering from deep lacerations or punctures should seek immediate emergency care.

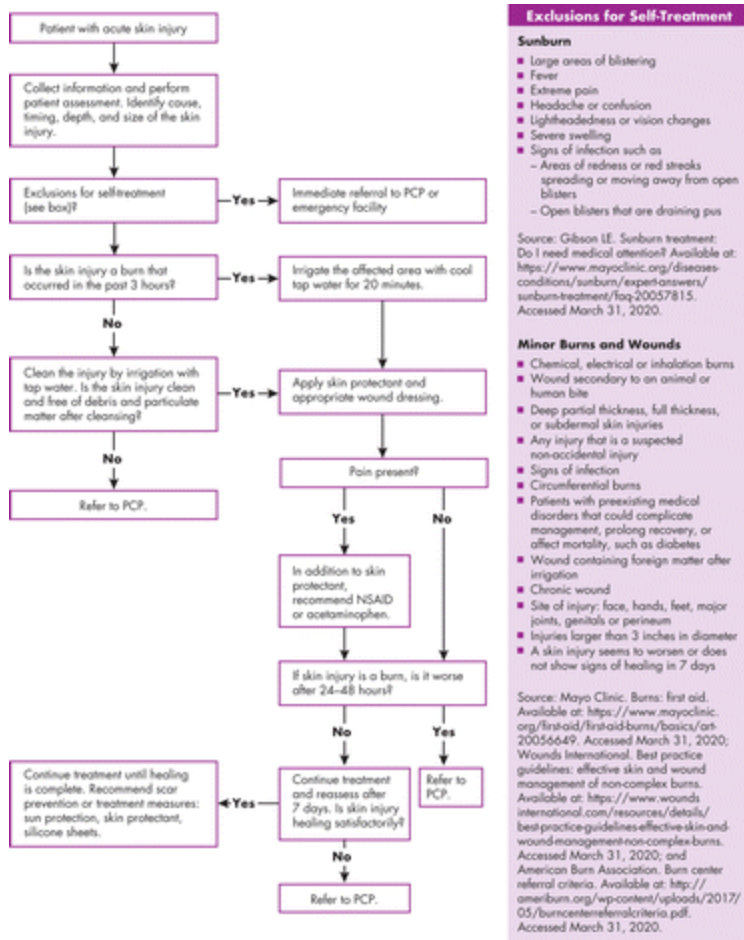
Determining the size of a skin injury also is critical to determining severity of an injury and whether self-care or referral is warranted. The rule-of-nines method is used to estimate body surface area (BSA) by dividing the body into multiples of 9%.¹² [Figure 41-4](#) illustrates the rule-of-nines method for estimating the percentage of affected BSA. Another method of BSA estimation involves using the patient's hand, including the palm of the hand and fingers, as the measuring tool to estimate 1% BSA.¹³



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FIGURE 41-4 Rule-of-nines method for quickly establishing the percentage of adult body surface burned. (Source: Adapted with permission from *The Guide to Fluid Therapy*. Deerfield, IL: Baxter Laboratories; 1969:111.)

Algorithm: Minor Burns and Sunburn



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FIGURE 41–3 Self-care for minor burns, sunburn, and wounds. Key: BSA = Body surface area; NSAID = nonsteroidal anti-inflammatory drug; PCP = primary care provider.

Treatment of Minor Burns, Sunburn, and Wounds

Treatment Goals

The goals in treating acute, minor skin injuries are (1) to relieve symptoms, (2) to promote healing by protecting the burn or wound from infection and further trauma, and (3) to minimize scarring.

General Treatment Approach

In addition to the typical assessment of the patient, the cause, timing, depth, and size of minor superficial and superficial partial-thickness burns and wounds should be assessed for self-treatment. When breaks in the skin are present, assessment of the patient's tetanus status should be performed.⁴ If the patient has none of the exclusions for self-treatment for burns or wounds (Figure 41-3), the provider should recommend appropriate measures using the treatment approach outlined in the algorithm.

Treatment of acute minor skin injuries classified as superficial and superficial partial thickness (e.g., abrasions, lacerations, burns) requires basic supportive measures, including cleansing the wound, applying moist wound care, and relieving any pain or discomfort. Wound cleansing by irrigation with cool, clean tap water is recommended.¹⁴ Wound dressings are not indicated for use in some superficial-thickness burns, such as minor sunburn; however, providing moisture to the affected skin through the use of agents such as non-perfumed, hypoallergenic skin protectants should be recommended first. The use of a wound dressing for superficial partial-thickness injuries is recommended to keep the area moist, and it may provide some pain relief and prevent entry of bacteria into the affected area.¹⁴⁻¹⁶ In addition, proper wound healing is the most significant way to minimize scarring. Pain management may be achieved with oral pain medications and soothing skin protectants. In sunburned patients, topical anesthetics may provide temporary pain relief.

Patient education, monitoring, and follow-up are crucial to self-care of skin injuries. The initial appearance of a burn injury often leads to an underestimate of its severity. The inflammatory response to a burn injury evolves over the first 24–48 hours; thus, a burn injury should be reassessed after 24–48 hours. The patient should be educated on signs and symptoms of infection, so it can be identified and treated immediately. In addition, patient education may be provided on methods to minimize scarring after the skin injury has healed.

Nonpharmacologic Therapy

Nonpharmacologic therapy for superficial and superficial partial-thickness skin injuries involves a variety of first-aid measures to prevent contamination, relieve pain, and promote healing.

Wound Cooling and Cleansing

Reducing further trauma to the site of a burn-induced skin injury is achieved by immediately removing the source of heat and actively cooling the burn wound with cool tap water. Running water is the treatment of choice because it is inexpensive and readily available in first-aid situations. Continuous cooling of the wound within the first 20 minutes of the injury slows the burning process, reduces pain, and diminishes the inflammatory response.¹⁷ Although this treatment is most beneficial immediately after a burn occurs, benefit may be found up to 3 hours after its occurrence.¹⁸ The application of ice or ice-cold water should be avoided because this measure may cause numbness and intense vasoconstriction, resulting in further tissue damage.

Wound cleansing is important to prevent infection and promote safe healing. Irrigation with clean tap water is the preferred method.^{14,17} Saline irrigation products (e.g., Simply Saline Wound Wash) provide no advantage over tap water when clean tap water is available. For uncontaminated wounds, cleansing through irrigation should be performed as gently as possible to avoid further injury. In contaminated injuries, more aggressive irrigation is warranted. If the patient is unable to remove foreign bodies or debris from the injury, referral to a primary care provider is warranted.¹⁴ Tetanus prophylaxis should be updated if needed.

Patients should be advised not to pull at loose skin or peel off burned skin because viable skin may be removed in the process, thereby delaying healing. If small blisters (<6 mm) are present, evidence shows they should be left intact to prevent infection and speed healing. Larger blisters and those located over mobile areas may rupture on their own. In this case, the area should be washed with soap and water and a moist wound dressing applied.^{4,19}

Wound Dressing

Historically, wound management involved leaving a wound open to air or covering it with a nonocclusive textile dressing (gauze). However, this type of management leads to scab formation, which impedes reepithelialization of wounds and may create unwanted scar tissue (Figure 41-5A). Wound dehydration may delay healing and increase risk of bacterial entry into the wound. Current treatment recommendations are based on creating a moist wound environment (Figure 41-5B). A moist healing environment stimulates

cell proliferation and encourages epithelial cells to migrate to heal the wound. Moisture-retentive dressings also act as a barrier to prevent infection and absorb excess wound fluid to prevent maceration of the skin from too much moisture. These dressings also can help decrease pain, reduce the need for frequent dressing changes, and provide autolytic debridement.^{19,20}

FIGURE 41–5 Mechanisms by which semipermeable wound dressings create a moist environment for wound healing. A, Regenerating epidermal cells are forced to “tunnel” below the dry wound scab to attain wound closure. This tunneling delays wound closure. B, Semipermeable wound dressings prevent formation of scab by maintaining optimal moisture level at the wound bed. Unhindered by the presence of a dry scab, migrating epithelial cells are able to migrate and close the wound. (Source: Adapted with permission from Syzcher M, Lee SJ. Modern wound dressings: a systemic approach to wounds. *J Biomater Appl.* 1992;7:142–213.)

Recommendations for a wound dressing depend on proper assessment of the skin injury. Some minor superficial-thickness skin injuries (e.g., sunburn, minor abrasion) may be treated successfully with a topical agent to promote healing, provide pain control, and prevent infection.¹⁴ In contrast, superficial partial-thickness injuries should be covered with a wound dressing. A nonadherent, hypoallergenic dressing may be applied to the wound to protect the damaged area and speed wound healing.

Types of Wound Dressings

Wound dressings continue to evolve with new product advancements. An understanding of the potential use and function of specific wound dressings will guide the provider in proper product selection. The focus of this chapter is treatment of minor acute wounds and burns; thus, wound dressings for use on chronic wounds such as alginates, foams, hydrogels, and collagens will not be addressed. [Table 41–1](#) provides examples of common types of acute wound care dressings.

TABLE 41-1 Selected Acute Minor Burn and Wound Dressings

Trade Names^a	Product Type	Advantages	Disadvantages
Sterilux Bulky Gauze Bandage Conform Kerlix Rolls and Sponges	Gauze dressings (nonocclusive fiber dressing with loose, open weave)	Readily available in many sizes Cost effective Highly absorbent for wounds with exudate Nonocclusive Conformable	Moist healing environment is not provided unless used with another product (e.g., skin protectant). Debridement is nonselective. Removal may cause bleeding/ pain. Secondary dressing (e.g., surgical tape, self-adherent wrap) is required to adhere to skin. Frequent dressing changes are required.
Adaptic Curad Non-stick Pads Nexcare Non-Stick Pads Vaseline Gauze	Nonadherent (gauze-type) dressings (nonadherent, lightly coated porous dressings)	Readily available Less adherent than plain gauze	Many do not provide moist healing environment. Secondary dressing (e.g., surgical tape or self-adherent wrap) is needed to adhere to skin. Removal may cause bleeding/ pain. Frequent dressing changes may be required.

Trade Names^a	Product Type	Advantages	Disadvantages
Band-Aid Flexible Fabric Adhesive Bandages Curad Flex- Fabric Adhesive Bandages	Adhesive Bandages (adhesive bandage with nonadherent pad in the center)	Readily available in a variety of shapes and sizes Cost effective Less adherent than plain gauze Special characteristics with some products, including clear bandages for discreet wound healing, waterproof adhesion, antibacterial fabric, cushioned fabric and highly durable adhesion	Many do not provide moist healing environment. Removal may cause bleeding/pain. Frequent dressing changes may be required.
Band-Aid Advanced Healing Strips DuoDERM CGF Dressing Medline Exuderm Wound Dressing Nu-Derm	Hydrocolloids (wafer dressings composed of hydrophilic particles in an adhesive form covered by a water-resistant film or foam)	Provide moist healing environment Manage exudate by particle swelling Long wear time Self-adherent Occlusive Impermeable to fluids/bacteria Protective Conformable Thermal insulation Reduce pain	Dressing is used for uninfected wounds only. Peri wound trauma may occur on removal. Dressings make assessment of wound difficult. Dressings are impermeable to gases. Some may leave residue on skin or in wound. Dressings are less cost effective.
Bioclusive Opsite Tegaderm	Transparent adhesive films (semioclusive, translucent dressings with partial or continuous adhesive composed of polyurethane or copolyester thin film)	Provide moist healing environment Self-adherent Semioclusive Gas-permeable Easy inspection of wound under dressing Impermeable to fluids/bacteria Protective Comfortable Reduce pain	Dressings are used for uninfected wounds only. Dressings are not absorptive. Peri wound trauma may occur on removal. With continuous adhesives, removal of

Trade Names ^a	Product Type	Advantages	Disadvantages
			bandage may reinjure wound. With large amounts of exudate, maceration may occur. Dressings are less cost effective.

^a Each trade-name product is an example of available products for each type of wound dressing. These products do not constitute an all-inclusive list of wound dressings.

Patients should be advised to keep the dressing clean and change the bandage according to the product directions. Ideally, wound dressing changes should be limited because it may damage the healing skin burn or wound. Dressing changes should occur if the dressing is dirty, foul smelling, or not adhering to the area.

Gauze is cost effective and readily available in a variety of forms including pads and rolls. Examples of gauze products are Curad Gauze Roll or Band Aid Gauze Pads. Gauze generally is used in the care of burns and wounds that are bleeding or draining or those requiring debridement. Traditional gauze products do not provide a moist environment; however, it can be impregnated with nonadherent products such as petrolatum, as well as with antiseptics and antimicrobials. Disadvantages of traditional gauze are that it must be held in place by a second agent, such as surgical tape or a self-adherent wrap. Some newer adhesive gauze products have the benefit of avoiding the use of a secondary agent (e.g., Band-Aid Cushion Care Adhesive Gauze Pads). Gauze must be changed often to prevent the wound from drying out. Removal of a traditional gauze dressing often tears away not only the scab but also the new tissue under the scab, potentially causing pain.²⁰ However, some improved gauze products are nonadherent to the wound (e.g., Band-Aid Hurt Free Non-Stick Pads), thereby limiting pain and tissue damage.

Adhesive bandages are cost-effective wound dressings that are used widely for minor acute skin injuries. However, many traditional adhesive bandages do not provide a moist healing environment; thus, a topical skin protectant should be recommended in conjunction with the adhesive bandage.¹⁵ Adhesive bandages are available in a variety of shapes and sizes. Product lines include characteristics to meet patients' needs, including clear bandages for discreet wound healing, waterproof adhesion, antibacterial fabric, cushioned fabric, and highly durable adhesion (e.g., Nexcare Waterproof Bandages, Band-Aid Infection Defense with Neosporin Bandages).

Hydrocolloid dressings consist of an inner colloidal layer composed of a combination of gel-forming agents and an outer water-impermeable layer. They provide a moist healing environment and are useful for partial-thickness wounds with minimal to moderate exudate. When hydrocolloids come in contact with moisture from the injury, they form gels and help protect the wound by absorbing excess exudate and by maintaining moisture.²¹ Hydrocolloid dressings also are indicated for the protection of intact skin, such as minor burns or blisters. Although hydrocolloid dressings are used most commonly in the management of chronic wounds, recognition of the importance of a moist wound healing environment has led to the development of hydrocolloid bandages for self-treatment of acute minor wound healing (e.g., Band-Aid Brand Hydro Seal bandages). However, hydrocolloid dressings often cost more than traditional adhesive bandages.

Transparent adhesive films (e.g., Nexcare Tegaderm Waterproof Transparent Wound Dressing Bandage) are thin, elastic, waterproof polyurethane films that are permeable to gas but impermeable to bacteria. Because these dressings are not highly absorbent, they are indicated for superficial-thickness and superficial partial-thickness wounds with minimal exudate. The flexibility of these dressings makes them suitable for difficult-to-cover areas such as joints like the elbow or knee. The transparency of some films allows inspection of wounds without removing the wound dressing.²²

Liquid adhesive bandages (e.g., New Skin Liquid Bandage, Nexcare Liquid Bandage Spray) are an alternative to conventional bandages for simple cuts and lacerations. They are applied by either spraying or brushing on the liquid, which then forms a clear, flexible coating over the injury. However, little evidence exists to document their effectiveness over other types of wound dressings for self-treatment of minor acute skin injuries.²³ Liquid adhesive

bandages may be preferred either for cosmetic considerations (e.g., a wound located on the face) or when a more flexible dressing product is needed (e.g., a wound located on the finger or elbow). They may have antibacterial or antiseptic properties. A slight burning sensation may occur upon their application. The adhesives are waterproof and have a high bonding strength; they may stay on for 5–10 days. Liquid adhesive bandages should not be used on large areas of the body, over sutures, near the eyes, or on mucous membranes.²⁴

Minimizing Scarring

Scarring that occurs secondary to a minor burn or wound can lead to negative physical, aesthetic, psychological, and social consequences for patients.²⁵ Patients should be advised that the most significant way to minimize scarring is to promote proper moist wound healing.²⁵ Strategies for proper wound healing are explained in the section “General Treatment Approach.” Research also has shown that UVR increases scar pigmentation and worsens the clinical appearance of scars.²⁶ Patients should be advised to avoid extensive UVR exposure and to take proper precautionary measures, including generous application of a sunscreen before going outdoors. (See [Chapter 39](#) for more information on prevention of sun-induced skin disorders.)

The latest guidelines for scar management advocate silicone therapy as the gold standard. Silicone therapy is the only noninvasive preventive and therapeutic measure for which there is adequate supporting data to make evidence-based recommendations. Silicone is believed to prevent and treat scars through occlusion and subsequent hydration of scar tissue.²⁷ Silicone products also may help relieve itching and discomfort that often accompanies scar formation. In minor burns and wounds, these products may be used to minimize the appearance of scarring only after the skin injury has fully healed. Silicone products also may be used on existing scars to help minimize their appearance. Nonprescription silicone products are available in sheet and gel formulations.

Silicone sheets consist of a soft, semi-occlusive gel sheet composed of medical-grade silicone and reinforced with a silicone membrane backing.²⁵ Examples of these products include ScarAway Silicone Scar Sheets and Embrace Active Scar Defense. Silicone sheets present benefits such as durability and ease of handling. However, their use may be limited because

they can be difficult to use on large areas or near joints, and many patients may be reluctant to use them on exposed areas of the body.

Silicone gel formulations (e.g., ScarAway 100% Silicone Scar Gel) have the same long-chain silicone polymer that is used in silicone sheets. The gel is applied in a thin layer to the skin where it dries and forms a transparent, flexible, gas-permeable, water-impermeable silicone coating.²⁵ Silicone gels present few barriers to use because they can be applied over areas of any size or near a joint.

Limited evidence is available for the use of topical products that are marketed specifically for minimizing the appearance of scars. One such product, Mederma, contains allantoin, a skin protectant, and onion extract. One trial that compared the efficacy of silicone gel, silicone sheets, and a topical product containing onion extract and allantoin found a statistically significant greater improvement in scar appearance after 6 months of treatment in both silicone treatment groups versus the onion extract/allantoin group.²⁸ Similarly, other products such as mitomycin C, green tea, aloe vera, and vitamins D and E have been proposed as options for scar treatment; however, literature supporting their use is lacking.²⁹ Therefore, silicone products should be recognized as the mainstay of therapy.

Finally, more invasive scar treatment options such as injections and laser therapy are available but are outside the scope of this text. Patients who are dissatisfied with the results of nonprescription treatment or who express interest in more extensive treatment should be referred to their primary care provider.

Pharmacologic Therapy

Various products are useful in treating minor acute burns, sunburn, and wounds. Agents may be used to protect the area from further damage or infection, relieve pain, cleanse the area, and/or aid in the healing process.

Systemic Analgesics

An initial step in treating pain from a minor skin injury is to recommend short-term administration of a systemic analgesic such as a nonsteroidal anti-inflammatory drug (NSAID) (e.g., aspirin, naproxen, ibuprofen) or

acetaminophen.¹⁰ Researchers hypothesized that NSAIDs, as prostaglandin inhibitors, could decrease the erythema and speed the healing time of sunburn; however, little evidence to support their use beyond symptomatic pain relief is available.^{10,17,18} (See [Chapter 5](#) for discussion of dosages and safety considerations for systemic analgesics.)

Skin Protectants

Skin protectants (e.g., Aquaphor Healing Ointment) are emollients and moisturizers that protect the injured area from irritation caused by friction and rubbing, and they prevent drying of the stratum corneum, thus promoting moist healing ([Table 41–2](#)). Skin protectants also make the injured area less painful. Application of skin protectants may differ depending on the type and extent of the skin injury. In two studies, application of Aquaphor (petrolatum) 2 and 3 times daily demonstrated superior effectiveness in wound healing compared with nonprescription antibiotic ointments.^{30,31} Skin protectants also are recommended for the prevention of scarring following wound re-epithelialization.¹⁴ Ingredients vary based on the manufacturer’s formulation, but some common skin protectant ingredients are petrolatum, white petrolatum, dimethicone, zinc oxide, glycerin, lanolin, cocoa butter, and colloidal oatmeal. These products should be free of fragrance and potential allergens. (See [Chapter 33](#) for more information on emollients and moisturizers.)

TABLE 41–2 Skin Protectant Products Commonly Used in Treatment of Minor Burns, Wounds, and Sunburn	
Trade Name ^a	Primary Ingredient
Aquaphor Healing Ointment	Petrolatum
CeraVe Healing Ointment	
Desitin Multi-Purpose Healing Ointment	White petrolatum
Vaseline Original 100% Pure Petroleum Jelly	
Neutrogena Norwegian Formula Hand Cream	Glycerin
Palmer’s Cocoa Butter Formula	Cocoa butter
Vaseline Intensive Care Cocoa Radiant	

Trade Name ^a	Primary Ingredient
Aveeno Itch Relief Balm with Colloidal Oatmeal	Colloidal oatmeal
Aveeno Soothing Bath Treatment with Colloidal Oatmeal	
Cetaphil Soothing Wash with Colloidal Oatmeal	

^a Each trade-name product is an example of available products for each type of skin protectant. This list of products does not constitute an all-inclusive list of products that contain these agents.

First Aid Antibiotics

Nonprescription first aid antibiotics consist of one or more of these active ingredients: bacitracin, neomycin, and polymyxin B sulfate. Examples of these products include Neosporin (bacitracin, neomycin, and polymyxin B sulfate) and Polysporin (bacitracin and polymyxin B sulfate). These topical agents are indicated for the prevention of infection in minor acute skin injuries. They are not indicated for the treatment of infected wounds. Many topical antibiotic products are formulated as an ointment, which helps in maintaining a moist healing environment.

Each of the three nonprescription antimicrobial agents has a unique mechanism of action, which gives a first aid triple antibiotic ointment a wide spectrum of activity. Bacitracin inhibits cell wall synthesis in several gram-positive organisms. Neomycin is an aminoglycoside antibiotic that inhibits protein synthesis in gram-negative bacteria and some *Staphylococcus* species. Polymyxin B sulfate causes leakage of intracellular constituents in gram-negative bacteria.

Available published research on the effectiveness of nonprescription topical antibiotics in wound healing and the prevention of infection is limited and conflicting. A systematic review of four randomized, controlled clinical trials found that topical antibiotics reduced the infection rate of acute, minor, uncomplicated soft tissue wounds.³⁰ In contrast, other studies that compared Aquaphor (a topical emollient) with nonprescription topical antibiotics showed that Aquaphor had superior or equivalent effectiveness in wound healing and prevention of infection.^{31–33} Potential drug resistance related to overuse of

antibiotics also must be considered.³¹ More data on the efficacy of topical antibiotics are needed to effectively determine their place in therapy.

Use of topical antibiotic products is primarily well tolerated and carries a risk of minimal hypersensitivity. Published data demonstrate a higher incidence of allergic contact dermatitis with the use of bacitracin and neomycin versus polymyxin B sulfate.³¹ When used, topical antibiotic preparations should be applied to the skin injury after cleansing and before applying a sterile dressing. This process should be performed 1–3 times a day. Application of these preparations on large areas of denuded skin requires special caution because the potential for systemic toxicity can increase.³⁴

Topical Anesthetics

Benzocaine and lidocaine are the topical anesthetics used most often in nonprescription products for temporary relief of pain from minor wounds, burns, and sunburns. Examples of these products include Dermoplast First Aid Spray (benzocaine 20%) and Alocane Severe Sunburn Gel (lidocaine 4%). Pramoxine is another topical anesthetic often added to nonprescription topical antibiotic ointments or moisturizers for its pain- and itch-relieving properties (e.g., CeraVe Moisturizing Cream for Itch Relief, Neosporin + Pain Relief Dual Action Cream). These products are available as gels, solutions, creams, ointments, and skin patches.³⁵ Because of the differences in drug delivery systems, the Drug Facts Label should be used to guide application of a product. More information on topical anesthetic products is available in [Chapter 37](#).

Topical anesthetics interrupt the transmission of electrical impulses along nerves by inactivating sodium channels in sensory neurons, thereby relieving pain and itch.³⁵ They have a rapid onset of action; their duration of action depends on the dose, route, and area of administration. However, in general, their physiological effects are fairly short-lived.³⁶ These products have the benefit of producing clinically effective drug concentrations at the site of the injury, without resulting in high systemic concentrations that can lead to adverse effects.³⁷

Few studies that examine the efficacy of topical anesthetic use in the outpatient setting are available. More research is needed to confirm the place of this drug class in therapy. Topical anesthetics appear to be effective options

for patients seeking pain relief from minor wounds, burns, and sunburns, but they may not be effective in relieving histamine-induced pruritus.^{38,39} The safety of these products also must be evaluated and considered before they are recommended to patients. Systemic absorption of benzocaine is associated with methemoglobinemia and, secondarily, with cyanosis, dyspnea, syncope, seizures, and coma.⁴⁰ Before patients use these drugs, they must be made aware of the appropriate clinical indications, safe concentrations and doses, and application instructions.

First Aid Antiseptics

Antiseptics destroy or inhibit the growth of microorganisms in tissue. Conversely, they can be cytotoxic to the cells essential for wound healing and reduce the healing rate in open skin injuries. Compared with topical antibiotics, antiseptics have a broader spectrum of antimicrobial activity and are more cytotoxic; however, antibiotics show a higher probability of occurrence of bacterial resistance.⁴¹ The presence of exudate, serum, and blood may diminish the effectiveness of antiseptics. Chlorhexidine (e.g., Hibiclens Skin Cleanser), hydrogen peroxide, and povidone–iodine solution (e.g., Betadine Antiseptic Solution) are examples of commonly available nonprescription antiseptics.

Antiseptics have been used in practice for many years; however, the management of acute and chronic wounds has changed significantly in the past decade. Evidence to support the use of antiseptics to prevent infections and promote healing in open wounds and burns is unclear. Strong evidence is available to support the use of clean tap water for wound irrigation to clean minor acute skin injuries as safe and effective.^{14,41–44}

Product Selection Guidelines

Ointments are oleaginous-based preparations. They provide a protective film to impede the evaporation of water from the wound area, which helps keep the skin from drying. If the skin is broken, an ointment may not be appropriate because of its impermeability. The presence of excessive moisture trapped beneath the ointment may promote bacterial growth or maceration of the skin, thereby delaying healing. Ointments are more appropriate for minor burns and wounds in which the skin is intact.

Creams are water-based emulsions that allow some fluid to pass through the film and are preferred for application to broken skin. Generally, creams are easier to apply and remove than ointments. To prevent contamination of the preparation, the patient should not apply ointments and creams directly from the container onto the burn or wound. A preferred technique is to apply the topical product to a clean or gloved hand or gauze and then apply it directly to the injury site.

Lotions spread easily and are easier to apply to a large burn or wound area. However, lotions that produce a powdery cover should not be used on a wound bed because they tend to dry out the area, are difficult (and possibly painful) to remove, and provide a medium for bacterial growth under the caked particles.

Generally, aerosol and pump sprays are more costly than other topical dosage forms. Sprays offer the advantage of precluding the need to physically touch the injured area, so the application process is associated with less pain. Proper application requires holding the container approximately 6 inches from the skin and spraying the wound area for 1–3 seconds. This method decreases the chances of chilling the area (from the aerosol). Sprays usually are not protective because the aerosol is typically water- or alcohol-based and will evaporate. In addition, alcohol-based sprays can irritate or dehydrate the wound bed.

Special Populations

Older adults are at increased risk of experiencing a minor wound, burn, or sunburn due to physiological changes associated with aging. Older adults have decreased surface contact between the dermis and epidermis, which predisposes the skin to separation of the dermal–epidermal junction. They also experience a significant reduction in cutaneous blood flow and dermal lymphatic drainage, which reduces the ability of the wound to clear itself of pathogens.⁴⁵ Therefore, it is important to educate older adults presenting with open wounds about the signs and symptoms of infection and the proper measures to take if these symptoms appear.

Professional attention is warranted for wounds in patients with diabetes. Poorly controlled diabetes is associated with reduced healing of acute wounds and a higher incidence of chronic non-healing diabetic foot ulcers.⁶ *Hyperglycemia*, or high blood glucose levels, alter white blood cell

function and increase the risk for infection.

Obesity is associated with various skin manifestations such as impaired wound healing and increased risk of skin infection.⁴⁶ When an obese patient presents with a wound in the outpatient setting, the cause of the wound should be determined. If the wound was caused by a potential complication of obesity (e.g., pressure wound, open wound within a skin fold), immediate referral to the primary care provider is warranted.

Although many pharmacologic agents can augment wound healing, some drugs can impair wound healing or even directly damage skin integrity. Medications reported to delay wound healing include anticoagulants, antimicrobials, antineoplastics, anti-rheumatoid medications, NSAIDs, colchicine, nicotine, steroids, and vasoconstrictors.⁸ Patients taking one or more of these medications who present with a minor wound or burn should be monitored closely and, if appropriate, referred to their primary care provider. Direct skin damage secondary to the use of a pharmacologic agent usually is a result of a hypersensitivity reaction.⁸ If a patient presents with dermatitis or open wounds and an allergic reaction is suspected, the patient should be referred to his or her primary care provider immediately.

Additional factors such as poor nutritional status, dehydration, and smoking can hinder healing of skin injuries.⁴⁵ Patients presenting with minor wounds, burns, and sunburn should be counseled on the importance of healthy eating, drinking adequate amount of water, and avoiding use of tobacco products to promote proper healing.

Complementary Therapies

Natural products commonly used for their healing properties include honey, aloe vera, and *Calendula officinalis*. (See [Chapter 51](#) for a more in-depth review of natural products for skin care.)

The use of honey in wound management dates back many centuries. Honey has reemerged as a treatment option for burn and wound management, and nonprescription delivery forms are commercially available (e.g., Derma Sciences Medihoney Paste Wound and Burn Dressing, Derma Sciences Products Medihoney Calcium Alginate Dressing). Honey is highly viscous and delivers a moist wound-healing environment. Because honey has high

osmolarity, it can absorb exudates from the wound, inhibit bacterial proliferation, and promote moist wound healing.⁴² Evidence suggests that honey can promote healing in partial-thickness burns.¹⁶ More research is needed to compare different kinds of honey and to develop recommendations for its routine use in clinical practice.

Aloe vera gel is obtained from the mucilaginous center of the leaf of the aloe vera plant. It has been used for many centuries and is the major ingredient in various commercial skin and wound care products. Although topical aloe vera is widely used as a nonprescription agent and is likely safe, available evidence does not support its use for healing of wounds and burns.⁴²

Calendula (as *C. officinalis*), also known as “pot marigold” is used widely for the treatment of many diseases, including burns, wounds, and dermatitis. It is thought to promote wound healing by its reported anti-inflammatory and antibacterial properties.⁴⁷ A recent review identified some evidence for the beneficial effects of calendula extract in wound healing; however, larger, well-designed randomized control trials are needed.⁴⁸

Assessment of Minor Burns, Sunburn, and Wounds: A Case-Based Approach

In addition to the review of the patient’s medication and medical history, the cause, timing (acute vs. chronic), depth, and size of minor superficial and superficial partial-thickness burns and wounds should be assessed for self-treatment.⁹ The injury also should be inspected for signs of contamination or infection. Visual inspection of the affected area usually provides an accurate evaluation of these factors and helps to determine whether self-treatment of the injury is appropriate. Acute skin injuries that fall into the depth classification ([Figures 41-1](#) and [41-2](#)) of superficial and superficial partial thickness may be appropriate for self-treatment if exclusions for self-treatment are absent.

Cases 41-1 and 41-2 provide examples of patient assessment for minor burns and wounds.

Case 41-1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient complains of a burn on his forearm that occurred when he took a pizza out of the oven about an hour ago. His burn is about an inch long and ¼ inch wide, not blistered but red and painful.
b. Description of any factors that seem to precipitate, exacerbate and/or relieve the patient's symptom(s)	The patient reports that the pain is constant, but running cool water over the burn provides temporary relief.
c. Description of the patient's efforts to relieve the symptoms	The patient held the burned area under cool running water, which helped decrease the pain slightly. He wants to know what he can do to help it heal quickly.
d. Patient's identity	John Pool
e. Age, gender, height, and weight	22 years old, male, 5ft 10 in., 165 lb
f. Patient's occupation	College student
g. Patient's dietary habits	Eats a regular diet.
h. Patient's sleep habits	7 hours nightly
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Omeprazole 20 mg daily for gastroesophageal reflux disease
j. Allergies	None
k. History of other adverse reactions to medications	None

Relevant Evaluation Criteria	Scenario/Model Outcome
I. Other (describe)	None
Assess	
2. Differentiate patient's signs/symptoms and correctly identify the patient's primary problem(s).	John is suffering from a minor burn due to thermal exposure from the pizza pan in the oven.
3. Identify exclusions for self-treatment.	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer the patient to an appropriate health care provider. (2) Recommend self-care with a nonprescription analgesic and nondrug measures. (3) Recommend self-care until the patient can see an appropriate health care provider. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	The patient can use self-care measures to treat his acute burn. He can use a nonprescription systemic analgesic, skin protectant, and nonadherent wound dressing.
6. Describe the recommended therapeutic approach to the patient or caregiver.	Rinse the burn with cool water for pain relief. Then gently pat the area dry, and apply a thin layer of a skin protectant to hold in moisture and protect the injury. Gently cover the area with a nonadherent wound dressing to further protect the area and to promote moist wound healing. If you are still experiencing pain, take a nonprescription systemic analgesic for pain relief.
7. Explain to the patient or caregiver the rationale for selecting the recommended	"Minor burns can be properly managed with nonprescription systemic analgesics and nonprescription skin protectants as long as there are no exclusions for self-

Relevant Evaluation Criteria	Scenario/Model Outcome
therapeutic approach from the considered therapeutic alternatives.	treatment, as in your case.”
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	See the box “Patient Education for Minor Burns and Sunburn.”
Solicit follow-up questions from the patient or caregiver.	“Should I apply triple antibiotic ointment to the burn?”
Answer the patient’s or caregiver’s questions.	“No. You do not need to apply triple antibiotic ointment because your risk of infection is very low.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome	“If you provide me with your phone number, I will give you a call in 7 days to see how you are healing.”

Case 41–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient’s symptoms and medical history, including	
a. Description of symptom(s)	The patient complains of a wound secondary to a dog bite on

Relevant Evaluation Criteria	Scenario/Model Outcome
(i.e., nature, onset, duration, severity, associated symptoms)	the back of her right calf. She was bitten by the neighbor's dog on her walk an hour ago. The area is red and swollen. One large puncture wound from the dog's teeth is visible, but the bleeding has stopped. The patient reports her pain as a 4 (on a scale of 1-10, with 10 being the worst).
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	The patient reports that she experiences slight pain when walking, and that the area is slightly tender to the touch.
c. Description of the patient's efforts to relieve the symptoms	She washed the wound with soap and water when she got home.
d. Patient's identity	Keisha Ford
e. Age, gender, height, and weight	47 years old, female, 5 ft 5 in, 140 lb
f. Patient's occupation	Teacher
g. Patient's dietary habits	Gluten-free diet
h. Patient's sleep habits	8 hours a night
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	None
j. Allergies	None
k. History of other adverse reactions to medications	None
l. Other (describe) -----	None
Assess	
2. Differentiate patient's signs/symptoms and	Keisha is suffering from a wound secondary to a dog bite.

Relevant Evaluation Criteria	Scenario/Model Outcome
correctly identify the patient's primary problem(s).	
3. Identify exclusions for self-treatment.	Wound secondary to animal bite
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer the patient to an appropriate health care provider. (2) Recommend self-care with a nonprescription analgesic and nondrug measures. (3) Recommend self-care until the patient can see an appropriate health care provider. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	The patient should consult her primary care provider.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"You should consult your primary care provider for treatment because self-treatment is not recommended for animal bites."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Wounds secondary to an animal bite require immediate medical attention to assess the need for systemic or topical antibiotics and potentially a tetanus booster to prevent infection. Seek medical help immediately."
Implement	
8. When recommending self-	Criterion does not apply in this case.

Relevant Evaluation Criteria	Scenario/Model Outcome
care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
Solicit follow-up questions from the patient or caregiver.	"Should I flush the wound with hydrogen peroxide to sterilize the area?"
Answer the patient's or caregiver's questions.	"No. Agents such as hydrogen peroxide cause damage to the injured skin and should be avoided. Cleanse the wound by irrigating it with running cool tap water. Gently pat it dry with a clean gauze pad. Apply a nonprescription first aid antibiotic or skin protectant, and cover the wound with a nonadherent wound dressing. See your primary care provider immediately to assess the need for further treatment.
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact the patient in 1-2 days to ensure that she sought proper medical care.

Patient Counseling for Minor Burns, Sunburn, and Wounds

Once a minor burn or wound is assessed as self-treatable, a discussion of cooling a burn and proper cleansing of a wound is appropriate. Ideally, cooling of a burn should occur immediately via irrigation with tepid tap water and last 20 minutes. However, this procedure is beneficial if it occurs within 3 hours after the burn occurred. Patients should be instructed to cleanse a wound through irrigation with tap water. Pain should be addressed and any necessary treatment recommendations provided. The patient should be advised how to promote moist wound healing, prevent infection, and, if needed, protect the injury with a skin protectant and wound dressing. Selection of a wound dressing should be based on wound characteristics. Patients should be

instructed to change a dressing only when it is soiled or not intact. Information on prevention of scarring with the use of skin protectants, prevention of UVR exposure, and application of silicone after the wound has healed also should be shared with the patient.

Because the inflammatory response to burns may evolve over the first 24–48 hours, follow-up for a burn injury should occur 24–48 hours after the injury to determine whether continuation of self-treatment or referral for further evaluation should be recommended. Patients should be educated on the signs and symptoms that indicate worsening of the injury. Minor acute superficial and superficial partial-thickness skin injuries should be healing satisfactorily by 7 days and fully healed by 14 days. Scar prevention and/or management may continue after the wound is healed. Medical referral for further evaluation is warranted if the skin injury does not show signs of healing after 7 days of self-treatment.

The box “Patient Education for Minor Burns, Sunburn, and Wounds” lists specific measures to provide patients to promote successful self-treatment for these injuries.

Patient Education for Minor Burns, Sunburn and Wounds

The objectives of self-treatment are (1) to relieve symptoms, (2) to promote healing by protecting the burn or wound from infection and further trauma, and (3) to minimize scarring. For most patients, carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

Nondrug Measures

- Treat superficial burns with no blistering as follows:
 - Irrigate the affected area with cool (not cold) tap water for 20 minutes.
 - If the patient did not cool the area in the first 20 minutes after the burn, benefit is still observed by cooling a burn up to 3 hours after it occurred.

- Cleanse the area with cool (not cold) tap water.
 - Apply a skin protectant and wound dressing to promote moist wound healing.
- For small burns with minor blistering, follow the first two steps above; then apply a dressing. A hydrocolloid dressing may best protect the blistered burn. If possible, avoid rupture of the blisters.
- For sunburns, avoid further sun exposure, and follow the previous procedures according to whether blistering is present.
- If a wound is dirty, irrigate it with tepid tap water or normal saline solution, which is not toxic to cells. If it still contains debris after irrigation, the patient should seek care from their primary care provider.
- Apply a skin protectant and cover the wound with a dressing that will keep the wound site moist. Make sure the dressing is the appropriate size and contour for the affected body part.
- Continue using a moist wound dressing until the wound bed has firmly closed and signs of inflammation in surrounding tissue have subsided. This process usually takes 1–2 weeks. Failure to keep the wound covered may delay healing.
- Avoid disrupting the dressing unnecessarily; change the dressing only if it becomes soiled or is not intact. More frequent changes may remove resurfacing layers of epithelium and slow the healing process.

Nonprescription Medications

- For minor acute burns, sunburn, and wounds, treat the affected area with a thin application of a skin protectant.
- Topical skin protectants, such as Aquaphor, may be as effective as topical antibiotics to promote moist wound healing and prevent infection.
- For temporary relief of pain, take acetaminophen, ibuprofen, or naproxen. (See [Chapter 5](#) for dosage guidelines and safety considerations.)
- If a topical anesthetic is used for pain relief, avoid use on large areas of the body to prevent systemic absorption.

Evaluation of Patient Outcomes for Minor Burns, Sunburn, and Wounds

Burns should be reassessed after 24–48 hours because the full extent of skin damage may not be apparent at the first counseling session. If the extent or severity of the burn has progressed or worsened, the patient should be referred to an appropriate health care provider for further evaluation.

Minor burns and wounds should exhibit decreased redness and inflammation during healing. Signs that indicate the need for further evaluation by a health care provider include evidence of cellulitis or tissue infection, such as increasing redness, pain, and swelling that extend beyond the boundaries of the original wound.

Follow up with the patient should occur after 7 days to assess the healing progress. If the burn or wound shows no signs of healing or has worsened in nature or degree (as indicated by a foul odor or increased inflammation), the patient should be referred to a health care provider.

Key Points for Minor Burns, Sunburn, and Wounds

- Minor acute superficial and superficial partial-thickness burns, sunburn, and wounds often can be treated with self-care measures.
- Moist wound healing is considered the standard of care.
- Burn injuries should be treated with cool (not cold) tap water for the first 20 minutes after the burn occurred, but benefit is seen with cooling the injury up to 3 hours after the burn.
- Burn injuries may increase in severity over the first 24–48 hours, so reassessment is necessary.
- Patient complaints usually focus on pain. Skin protectants and

moist wound dressings should be recommended, and NSAIDs or acetaminophen may be helpful.

- Proper selection of first aid products, including appropriate wound dressing, is essential.
- Blisters should not be ruptured. If large blisters are present, the patient should be referred for medical treatment.
- Skin protectants, such as Aquaphor, are as effective as first aid antibiotics in promoting moist wound healing and preventing infection.
- Moist wound healing is critical for scar prevention. Use of skin protectants or silicon and prevention of sun exposure are useful for preventing and treating scars.

Chapter 42: Fungal Skin Infections

Authors: Megan G. Smith

Approximately 20%–25% of the world’s population suffers from fungal skin infections, including dermatophyte, non-dermatophyte, and candidal infections, with dermatophyte fungi being responsible for a majority of the cases.^{1,2} Most fungal infections are a result of a barrier breakdown in either the skin or nail or an associated comorbid condition affecting host defense mechanisms, including diabetes, obesity, and/or an immunocompromised state.^{1,3}

Fungal infections usually are superficial and can involve the hair, nails, and skin. The term *tinea* refers exclusively to dermatophyte infections. Most often, tinea infections are named according to the area of the body that is affected (e.g., scalp [tinea capitis]; groin [tinea cruris]; body [tinea corporis]; feet [tinea pedis]; nails [tinea unguium]).

Although many pathogenic fungi are recognized, the overall prevalence of actual superficial fungal infections is remarkably low. An estimated 10%–20% of the U.S. population will suffer from a tinea infection at any one time.^{4,5} Differing degrees of susceptibility, ranging from instantaneous “takes” by a single spore to severe trauma with massive exposure, can lead to clinical infection. Trauma to the skin, especially producing blisters (e.g., from wearing ill-fitting footwear), appears to be significantly more important than simple exposure to the offending pathogens.^{5,6}

In addition to specific fungi, other environmental factors, such as climate and social customs, contribute to dermatophytosis development. Footwear is a key variable, as illustrated by the notable incidence of tinea pedis in wearers of occlusive footwear, especially in the summer and in tropical or subtropical climates. Nonporous shoe material increases temperature and hydration of the skin, which interferes with the barrier function of the stratum corneum. Similarly, sweating and wearing wet clothing for long periods of time are predisposing factors for the development of tinea corporis and tinea cruris.

Other factors associated with the development of tinea infections include diabetes and other autoimmune diseases, use of immunosuppressive drugs, impaired circulation, and poor nutrition and hygiene.^{5,6} For example, patients

with diabetes or human immunodeficiency virus infection and older persons taking medications such as glucocorticoids should be instructed to self-monitor for signs and symptoms of tinea infections. The importance of proper hygiene and diet for prevention of tinea infections and other health problems also should be emphasized.

The most prevalent cutaneous fungal infection in humans is *tinea pedis*—dermatophytosis of the foot, or athlete's foot. Tinea pedis afflicts approximately 26.5 million people in the United States every year; 7 of every 10 persons affected are male. Approximately 45% will suffer with tinea pedis episodically for longer than 10 years. When exposure to infectious environments is equal, the incidence of tinea pedis infections in women approaches that in men.^{4–8} Tinea pedis is rare among blacks but common in whites, particularly those who live in urban tropical areas.⁹ An estimated 70% of people will be afflicted with tinea pedis in their lifetime. Although tinea pedis may occur at all ages, it is more common in adults, presumably because of the increased opportunities for exposure to pathogens in this age group.⁵

The risk for development of tinea pedis is greater in persons who use public pools or bathing facilities than in the general population. However, tinea pedis may be acquired in the home if one or more members of the household are already infected. High-impact sports that cause chronic trauma to the feet (e.g., long-distance running) also predispose athletes to the development of tinea pedis.^{4,5,10} The trauma affords pathogenic fungi the opportunity to invade the outer layers of the skin. In addition, wearing socks and shoes exacerbates the problem by impeding the dispersion of heat and the evaporation of moisture, both of which facilitate fungal growth. By contrast, people who most often use footwear that allows the feet to remain cool and dry (e.g., sandals) are less likely to develop tinea pedis.⁴

Tinea unguium—ringworm of the nails, or onychomycosis—causes about one half of all nail disorders and is sometimes associated with tinea pedis. The prevalence of tinea unguium is approximately 14%, and the incidence among children also has increased to approximately 20% of diagnosed dermatophyte infections.^{5,11} The U.S. Food and Drug Administration (FDA) has not approved topical self-treatment for onychomycosis. Rather, the condition must be treated with systemic prescription drug therapy (e.g., terbinafine, itraconazole), prescription combination topical (e.g., ciclopirox olamine 8% or efinaconazole 10% nail solutions) and systemic oral therapy, or surgical removal of the

affected nail.¹²

The next two most common fungal infections are tinea corporis and tinea cruris. *Tinea corporis*, also called ringworm of the body, is most common in the prepubescent age group. It is frequently transmitted among children in daycare centers and among teenage and younger athletes who participate in contact sports, such as wrestling. Additionally, this form of ringworm is more prevalent overall in adults and children who live in hot, humid climates. Persons who are under stress, overweight, or immunosuppressed also are at increased risk for development of tinea corporis.^{1,5,13}

Tinea cruris, or jock itch, often manifests as a pruritic, red rash and is most common during warm weather; however, it can occur at any time of the year if the skin in the groin area stays warm and moist for long periods. For example, sweating or prolonged contact with wet clothing provides ideal conditions for the growth of fungi. Tinea cruris occurs up to three times more often in men than in women and rarely affects children.⁵ Close indirect or direct physical contact between infected males and noninfected females does not mitigate the higher prevalence of tinea cruris in males. For example, females who live in the same household with infected males do not develop infections at the same rate as for noninfected males in the same household.⁵

Although its true incidence is unknown, *tinea capitis*, or ringworm of the scalp, occurs most often in children, both because their likelihood of having contact with infected persons is higher and because they are less attentive than adults to personal hygiene. Tinea capitis is the most common dermatophyte infection in children 3–14 years of age.^{5,10} Compared with black males and white children, black female children are infected more often, possibly because of the hair care products and practices (e.g., occlusive hair dressings, tight braiding) that are unique to this population.^{5,13} Tinea capitis can be spread by direct contact with an infected person, but spread often occurs by contact with infected fomites (e.g., using infected combs, toys, or telephones; wearing infected clothing or hats; using contaminated towels; sleeping on infected linens). In some instances, tinea capitis is spread through contact with other infected persons or with infected cats or dogs.¹⁴ As with onychomycosis, tinea capitis cannot be managed with nonprescription antifungals.

Pathophysiology of Fungal Skin Infections

Tinea infections are caused by three genera of pathogenic fungi: *Trichophyton*, *Microsporum*, and *Epidermophyton*.^{3,12,15} Tinea pedis and tinea cruris are caused by species of *Epidermophyton* and *Trichophyton*. Species of *Trichophyton* and *Microsporum* cause ringworm of the scalp. *Trichophyton* species also cause onychomycosis. Fungi of all three genera can cause tinea corporis, although *Trichophyton* is most common.⁵

Dermatomycoses often are referred to as ringworm because their characteristic lesions are ring-shaped, with clear centers and red, scaly borders. However, morphologic features can vary, and clinical findings may include single or multiple lesions that range from mild scaling to deep *granulomas* (inflamed, nodular lesions). The most common causative agents of dermatomycoses are *Trichophyton rubrum*, *Trichophyton tonsurans*, and *Trichophyton mentagrophytes*. *T. rubrum* is the most commonly isolated dermatophyte in the United States.^{1,10} Non-dermatophytes and species of *Candida* and other yeasts also may be involved in fungal skin infections; however, no nonprescription antifungals are currently available for self-management of cutaneous infections due to yeasts.¹⁶

Fungal transmission can occur through contact with infected people, animals, soil, or fomites. Dermatophytes are classified according to their natural habitat: anthropophilic (humans), zoophilic (animals), and geophilic (soil). Most tinea infections are caused by person-to-person contact with patients infected with anthropophilic dermatophytes.¹³

After a dermatophyte is inoculated into the skin under suitable conditions, a tinea infestation progresses through several stages: After an initial period of incubation, the infection progresses through stages of adherence and penetration, followed by a refractory period and a stage of involution. During the incubation period, the dermatophyte grows in the stratum corneum, sometimes with minimal signs of infection. After the incubation period and once the infection is established, two factors appear to play a role in determining the size and duration of the lesions: the growth rate of the organism and the epidermal turnover rate.¹⁷ The fungal growth rate must equal or exceed the epidermal turnover rate; otherwise the organism will be quickly shed.

Clinical Presentation of Fungal Skin

Infections

The clinical spectrum of tinea infections ranges from mild itching and scaling to a severe, exudative inflammatory process characterized by denudation, fissuring, crusting, and/or discoloration of the affected skin. Persons experiencing their first tinea infection and patients with infections secondary to zoophilic fungi tend to present with a greater degree of inflammation.¹³ **Table 42–1** summarizes key differences among fungal skin infections, contact dermatitis, and bacterial skin infections, to distinguish the underlying cause of a patient’s symptoms from other conditions that may have a similar clinical presentation.

TABLE 42–1 Differentiation of Fungal Skin Infections and Skin Disorders With Similar Presentations

Criterion	Fungal Skin Infection	Contact Dermatitis	Bacterial Skin Infection
Location	On or in areas of the body where excess moisture accumulates, such as the feet, groin, scalp, and underarms	Any area of the body exposed to the allergen/irritant; hands, face, legs, ears, eyes, and anogenital area most often involved	Anywhere on the body
Signs	Manifests either as soggy malodorous, thickened skin; acute vesicular rash; or fine scaling of affected area with a variable degree of inflammation; cracks and fissures in more severe cases	Manifests as a variety of lesions: raised wheals, fluid-filled vesicles, or both	Manifests as a variety of lesions, from macules to pustules to ulcers with surrounding redness; lesions often warmer than surrounding, unaffected skin
Symptoms	Itching and pain	Itching and pain	Irritation and pain
Distribution	Usually localized to a single region of the body but can spread	Affects all areas of exposed skin but does not spread	Usually localized to a single region of the body but can spread
Timing	Variable onset after exposure	Variable onset from immediately after exposure to 3	Variable onset after exposure

Criterion	Fungal Skin Infection	Contact Dermatitis	Bacterial Skin Infection
		weeks after contact	
Cause	Superficial fungal infection	Exposure to skin irritants or allergens	Superficial bacterial infection
Modifying factors	Treated with nonprescription astringents, antifungals, and nondrug measures to keep the area clean and dry	Treated with topical antipruritics, skin protectants, astringents, and nondrug measures to avoid reexposure	Treated with prescription antibiotics

Tinea Pedis

Clinically, tinea pedis has four accepted variants; two or more of these types may overlap. The most common is the *chronic interdigital* type,⁵ characterized by fissuring, scaling, or maceration in the interdigital spaces; malodor; pruritus; and/or a stinging sensation on the feet (see [Color Plates](#), photograph 31).

Typically, the infection involves the lateral toe webs, usually between either the fourth and fifth or the third and fourth toes. From these sites, the infection may spread to the sole or instep of the foot but rarely to the dorsum. Warmth and humidity aggravate this condition; if present, *hyperhidrosis* (excessive sweating) then becomes a major contributing factor and must be addressed along with the dermatophyte infestation.⁵

After initial invasion of the stratum corneum by dermatophytes, enough moisture may accumulate to trigger bacterial overgrowth. Increased moisture and temperature then lead to the release of metabolic products that readily diffuse through the underlying horny layer already damaged by fungal invasion. In more severe cases, gram-negative organisms intrude and may exacerbate the condition, causing skin maceration, white hyperkeratosis, or erosions with worsening symptomatology.⁵

The second variant of tinea pedis is the *chronic hyperkeratotic* type.⁹ It usually involves both feet and is characterized by mild inflammation and diffuse scaling in a moccasin-like distribution on the soles and lateral and medial aspects of the feet. Tinea unguium of one or more toenails also may be present and may continue to fuel the infection.

The third variant of tinea pedis is the *vesicular* type, usually caused by *T. mentagrophytes* var. *interdigitale*.¹⁵ Small vesicles or vesicopustules are observed near the instep and on the mid-anterior plantar surface. Skin scaling is seen in these areas as well as on the toe webs. This variant is symptomatic in the summer and is clinically quiescent during the cooler months.

The *acute ulcerative* type is the fourth and least common variant of tinea pedis. It often is associated with macerated, denuded, weeping ulcerations on the sole of the foot. Typically, white hyperkeratosis and a pungent odor are present. The term *dermatophytosis complex* has been used to describe this type of infection, which is complicated by an overgrowth of opportunistic, gram-negative bacteria such as *Proteus* and *Pseudomonas*. Such infections may feature one or more extremely painful, erosive, purulent interdigital spaces that can impede the patient's ability to walk.⁵

Tinea Unguium

Nails affected by tinea unguium gradually lose their normal shiny luster and become opaque. If left untreated, the nails become thick, rough, yellow, opaque, and friable. The nail may separate from the nail bed if the infection progresses secondarily to subungual hyperkeratosis. Ultimately, the nail may be lost altogether. Subungual debris also provides an excellent medium for the growth of opportunistic bacteria and other microorganisms, which can lead to further infectious complications.⁵

Tinea Corporis

Tinea corporis may have diverse clinical manifestations. Most often, the lesions, which involve *glabrous* (smooth and bare) skin, begin as small, circular, erythematous, scaly areas. The lesions spread peripherally, and the borders may contain vesicles or pustules. Infected persons also may complain of pruritus.¹⁸

Tinea corporis can occur on any part of the body. However, the location of the infection can provide clues to the type of infecting dermatophyte. For example, zoophilic dermatophytes often infect areas of exposed skin such as the neck, face, and arms. By contrast, infections secondary to anthropophilic dermatophytes often occur in occluded areas or in areas of trauma.⁵

Tinea Cruris

Tinea cruris is more common in males and occurs on the medial and upper parts of the thighs and the pubic area. The lesions have well-demarcated margins that are slightly elevated and are more erythematous than the central area; small vesicles may be seen, especially at the margins. Acute lesions are bright red, and in chronic cases the skin tends to have a more hyperpigmented appearance; fine scaling usually is present. This condition generally is bilateral, with significant pruritus; of note, however, the lesions usually spare the penis and scrotum. The characteristic lack of involvement of these areas can help to distinguish tinea cruris from candidiasis, which more typically affects the entire region.¹⁹ Pain also may be present during periods of sweating or when the skin becomes macerated or infected by a secondary microorganism.^{4,5}

Tinea Capitis

Clinically, tinea capitis may manifest as one of four variant patterns, depending on the causative dermatophyte. In *noninflammatory* tinea capitis, lesions begin as small papules surrounding individual hair shafts. Subsequently, the lesions spread centrifugally to involve all hairs in their path. Although there is some scaling of the scalp, little inflammation is present (see [Color Plates](#), photograph 32). Hairs in the lesions are a dull gray color and usually break off above the scalp level.⁵

The *inflammatory* type of tinea capitis produces a spectrum of inflammatory changes ranging from pustules to kerion formation. *Kerions* are weeping lesions whose exudate forms thick crusts on the scalp.⁸ In addition to fever and pain, patients with this type of tinea capitis may experience more intense pruritus. Regional lymph nodes also may be enlarged.⁵

The *black dot* variety of tinea capitis was named for the appearance of infected areas of the scalp. The location of arthrospores at the base of the hair shaft causes hairs to break off at the level of the scalp, leaving black dots on the scalp surface. Hair loss, inflammation, and scaling with this type of tinea capitis range from minimal to extensive. Therefore, this variant is especially challenging to diagnose.^{5,20,21}

The *favus* variant of tinea capitis typically manifests as patchy areas of hair loss and *scutula* (yellowish crusts and scales). Ultimately, these lesions can coalesce

to involve a major portion of the scalp. If left untreated, this condition can lead to secondary bacterial infections, scalp atrophy, scarring, and permanent hair loss.⁵

Treatment of Fungal Skin Infections

Overall, fungal skin infections do not have a significant impact on mortality; however, they can be difficult to treat, leading to chronic lesions and a decrease in quality of life.¹⁵

Treatment Goals

The goals of self-treatment for fungal skin infections are (1) to provide symptomatic relief, (2) to eradicate existing infection, and (3) to prevent future infections.

General Treatment Approach

In many instances, effective self-treatment for tinea pedis, tinea corporis, and tinea cruris can be achieved with nonprescription topical antifungals and nonpharmacologic measures. However, persons with tinea unguium or tinea capitis should be referred to their primary care provider or a dermatologist for treatment.

Before recommending therapy, the health care provider must be reasonably sure that the lesions are consistent with a tinea infection. Their appearance should conform to the descriptions provided in the section “Clinical Presentation of Fungal Skin Infections,” and the [Color Plates](#) photographs 31 and 32 of tinea lesions should be consulted for comparison. Furthermore, the lesions should not resemble any other skin conditions. When the true cause of a condition is in doubt, the patient should be advised to consult a dermatologist or other knowledgeable health care provider. [Figure 42–1](#) outlines appropriate self-treatment options for fungal skin infections.

A number of topical antifungals are available in a variety of dosage forms for self-treatment for fungal skin infections. The selection of a particular product depends on the type of infection and on individual patient characteristics and preferences. For example, in acute inflammatory tinea pedis, characterized by

reddened, oozing, and vesicular eruptions, the inflammation must be counteracted with solutions of astringent aluminum salts before antifungal therapy can be instituted.

A critical determinant of the outcome of therapy is the patient's ability to adhere to the recommended treatment regimen for the appropriate length of time. Adherence may be difficult, because these conditions may take between 2 to 6 weeks to resolve ([Table 42-2](#)). Patients may be tempted to terminate therapy when their symptoms subside but before the infection has been eradicated.

TABLE 42-2 Selected Nonprescription Topical Antifungal Products

Trade Name	Active Ingredient	Indications for Use	Directions for Use
Desenex Antifungal Powder	Miconazole 2%	For adults and children older than 2 years of age	For jock itch and ringworm, apply twice daily for 2 weeks.
			For athlete's foot, apply twice daily for 4 weeks.
Lotrimin AF Jock Itch Antifungal Powder Spray	Miconazole 2%	For adults and children older than 2 years of age	For athlete's foot and ringworm, apply twice daily for 4 weeks.
			For jock itch, apply twice daily for 2 weeks.
Micatin Antifungal Cream	Miconazole 2%	For adults and children 2 years of age and older	For athlete's foot and ringworm, apply twice daily for 4 weeks.
			For jock itch, apply twice daily for 2 weeks.
Lotrimin AF Clotrimazole Jock Itch Cream	Clotrimazole 1%	For adults and children 2 years of age and older	For athlete's foot and ringworm, apply twice daily for 4 weeks.
			For jock itch, apply daily for 2 weeks.
Lotrimin	Butenafine	For adults	For athlete's foot between the toes, apply twice

Trade Name	Active Ingredient	Indications for Use	Directions for Use
Ultra Jock Itch Cream	1%	and children 12 years and older	daily for 1 week, or once daily for 4 weeks.
			For jock itch and ringworm, apply once daily for 2 weeks.
Lamisil AT (cream, spray)	Terbinafine 1%	For adults and children 12 years and older	For athlete's foot between the toes, apply twice daily for 1 week.
			For jock itch and ringworm, apply once daily for 1 week.
Tinactin Athlete's Foot Cream	Tolnaftate 1%	For adults and children 2 years of age and older	For athlete's foot and ringworm, apply daily for 4 weeks.
			For jock itch, apply daily for 2 weeks.
Tinactin Powder Spray	Tolnaftate 1%	For adults and children 2 years of age and older	For athlete's foot and ringworm, spray twice daily for 4 weeks.
			For prevention, spray 1-2 times daily.
Fungicure (solution, cream)	Undecylenic acid 10%, 22%, 25%	For adults 18 years of age and older	For ringworm and athlete's foot, apply twice daily for 4 weeks.
Hypercare	Aluminum chloride	For adults with hyperhidrosis	Apply daily at bedtime; once excessive sweating has stopped, decrease to once or twice weekly or as needed.
Domeboro	Aluminum acetate	Temporary relief of minor skin irritation	<i>Soak:</i> Soak affected area in solution for 15-30 minutes as needed. May repeat 3 times daily.
			<i>Wet dressing:</i> Soak a clean, soft, white cloth in solution and apply loosely to affected area for 15-30 minutes; may repeat as needed for 4 to 8 hours.

Nonpharmacologic Therapy

Another determinant of therapeutic outcome is the patient's adherence to recommended nonpharmacologic measures recognized as important components of management of fungal infections, for both treatment and prophylaxis. These measures include keeping the skin clean and dry, avoiding the sharing of personal articles, and avoiding contact with infected fomites or persons who have a fungal infection.

The box "Patient Education for Fungal Skin Infections" describes nonpharmacologic measures intended to complement the effects of nonprescription antifungals and to prevent future infections. The patient should follow these measures during and after treatment of the infection.

Pharmacologic Therapy

An antifungal agent or ingredient must have at least one well-designed clinical trial that demonstrates its effectiveness in treating tinea infections before FDA will classify it as an approved agent for inclusion in the antifungal monograph.²² Clotrimazole, miconazole nitrate, terbinafine hydrochlorate, butenafine hydrochloride, tolnaftate, and undecylenic acid are considered safe and effective nonprescription topical agents for the treatment of fungal skin infections.¹⁶ Rare cases of mild skin irritation, burning, and stinging have occurred with use of nonprescription topical antifungals. These agents are labeled for treatment of athlete's foot, jock itch, and body ringworm. Nystatin (prescription only) is effective only for yeasts, not dermatophytes, and therefore should not be used for tinea infections.²³

Clotrimazole and Miconazole Nitrate

Topical clotrimazole and miconazole nitrate are imidazole derivatives that demonstrate fungistatic/fungicidal activity (depending on concentration) against *T. mentagrophytes*, *T. rubrum*, *Epidermophyton floccosum*, and *Candida albicans*.

These agents act by inhibiting the biosynthesis of ergosterol and other sterols and by damaging the fungal cell wall membrane, thereby altering its permeability and resulting in the loss of essential intracellular elements. These drugs also have been shown to inhibit the oxidative and peroxidative enzyme

activity that results in intracellular buildup of toxic concentrations of hydrogen peroxide; this toxicity may then contribute to the degradation of subcellular organelles and to cellular necrosis. In *C. albicans* infections, these drugs have been shown to inhibit the transformation of blastospores into the invasive mycelial form that causes infection.

FDA classifies clotrimazole 1% and miconazole nitrate 2% as safe and effective for topical nonprescription use in treating tinea pedis, tinea cruris, and tinea corporis. Clotrimazole and miconazole nitrate are applied twice daily. For athlete's foot and ringworm, these drugs should be applied twice daily for 4 weeks; for jock itch, they should be applied twice daily for 2 weeks.

A drug–drug interaction between warfarin and topical miconazole cream is possible: Coadministration of the drugs may increase the effects of warfarin.²⁴ No other drug–drug interactions have been reported with topical use of clotrimazole and miconazole nitrate for up to 4 weeks.¹⁶

Terbinafine Hydrochloride

Topical terbinafine hydrochloride 1% is an allylamine antifungal agent that inhibits squalene epoxidase, a key enzyme in fungal sterol biosynthesis. This inhibiting effect results in a deficiency in ergosterol and a corresponding accumulation of squalene within the fungal cell, causing fungal cell death. Terbinafine hydrochloride is indicated for interdigital tinea pedis, tinea cruris, and tinea corporis caused by *E. floccosum*, *T. mentagrophytes*, and *T. rubrum*. Similar to miconazole and clotrimazole, terbinafine hydrochloride should be applied sparingly to the affected area twice daily.

In clinical trials, this drug was demonstrated to provide mycologic cure of tinea pedis with 1 week of treatment. However, complete resolution of symptoms may require up to 4 weeks of treatment. For athlete's foot between the toes, terbinafine should be applied twice a day for 1 week. For athlete's foot on the bottom or sides of the foot, it should be applied twice a day for 2 weeks. For jock itch and ringworm, patients should apply terbinafine once a day for 1 week or as directed by the patient's primary care provider.

Clinical trials to date have demonstrated a low incidence of adverse effects for terbinafine hydrochloride. Such effects include irritation (1%), burning (0.8%), and itching/dryness (0.2%).^{25,26} No drug–drug interactions have been reported with topical use of this agent.

Butenafine Hydrochloride

Topical butenafine hydrochloride 1% also is an antifungal squalene epoxidase inhibitor. This mechanism of action results in a deficiency in ergosterol, a corresponding accumulation of squalene within the fungal cell, and eventually cell death.

Butenafine hydrochloride is indicated as a clinical and mycologic cure for tinea pedis between the toes, tinea cruris, and tinea corporis caused by *E. floccosum*, *T. mentagrophytes*, and *T. rubrum*. Similar to other nonprescription topical antifungals, butenafine hydrochloride also relieves the itching, burning, cracking, and scaling that can accompany these conditions. This agent's effectiveness for eradicating infection of the bottom or sides of the foot is unknown.

Patients suffering from tinea pedis should be advised to apply a thin film to affected skin between and around toes twice daily for 1 week or once a day for 4 weeks, based on patient preference, or as directed by the patient's primary care provider. Patients with tinea cruris or tinea corporis should apply a thin film to the affected area once daily for 2 weeks or as directed by the primary care provider.

Effective treatment rates of butenafine for interdigital tinea pedis with 1-week and 4-week application durations are reported to be approximately 38% and 74%, respectively. In clinical trials, butenafine kept users free of tinea pedis for up to 3 months.²⁷ To date, clinical trials demonstrate a low incidence of adverse effects, limited to burning and itching, for this agent.^{27,28} Furthermore, no drug–drug interactions have been reported with its topical use.

Tolnaftate

Topical tolnaftate has demonstrated clinical efficacy since its commercial introduction in the United States in 1965. In addition, for many years, it was the standard against which the efficacy of other topical antifungals was compared. Tolnaftate is approved for treatment of tinea pedis, tinea cruris, and tinea corporis.

Although tolnaftate's exact mechanism of action has not been reported, tolnaftate is thought to distort the hyphae and stunt the mycelial growth of the fungi species. Tolnaftate is the only nonprescription drug approved for

both preventing and treating tinea infections.¹⁶ It acts on fungi that are typically responsible for tinea infections, including *T. mentagrophytes*, *T. rubrum*, and *E. floccosum*.

Tolnaftate is valuable primarily in treating the dry, scaly lesions. Relapse of superficial fungal infections has occurred after discontinuation of tolnaftate therapy. Relapse may be caused by inadequate duration of treatment, patient nonadherence with the medication, or use of tolnaftate when an oral antifungal should have been used.

As a cream, tolnaftate is formulated in a polyethylene glycol 400/propylene glycol vehicle. The 1% solution is formulated in polyethylene glycol 400 and may be more effective than the cream. The solution solidifies when exposed to cold but liquefies with no loss in potency if allowed to warm. These vehicles are particularly advantageous in superficial antifungal therapy, because they are nonocclusive, nontoxic, nonsensitizing, water-miscible, anhydrous, easy to apply, and efficient in delivering the drug to the affected area.

The topical powder formulation of tolnaftate uses cornstarch/talc as the vehicle. The two agents combined absorb excess moisture in the affected area that allows fungus to thrive. The topical aerosol formulation of tolnaftate includes talc, alcohol, and the propellant vehicle.

Tolnaftate (1% solution, cream, gel, powder, spray powder, or spray liquid) is applied sparingly twice daily. Effective therapy usually takes 2–4 weeks, depending on the type of infection. For example, a patient should experience improvement of symptoms with tinea cruris within 2 weeks, but treatment for tinea pedis and tinea corporis may take 4–6 weeks. Tolnaftate is well tolerated when applied to intact or broken skin, although it usually stings slightly when applied. Delayed hypersensitivity reactions to tolnaftate are extremely rare. No drug–drug interactions have been reported with topical use of tolnaftate.

Undecylenic Acid

Undecylenic acid is an antifungal fatty acid providing astringent action that reduces rawness and irritation. It is commercially available as a solution that contains undecylenic acid 25%. For tinea pedis and corporis, it is applied twice daily for 4 weeks. For tinea cruris, it is applied twice daily for 2 weeks. Common adverse effects include local skin irritation and burning sensations. There are no known significant drug–drug interactions.

Salts of Aluminum

Because aluminum salts do not have any direct antifungal activity, these drugs are not included in the FDA final monograph for topical antifungal drug products. Rather, they are approved for the relief of inflammatory conditions of the skin, such as tinea pedis. However, their effectiveness as astringents and their possible use in treating tinea pedis merit their inclusion in this chapter. Historically, aluminum acetate has been the foremost astringent used for both the acute, inflammatory type and the wet, soggy type of tinea pedis. Aluminum chloride is also used to treat the wet, soggy type of infection.

Aluminum salts do not provide a definitive cure for athlete's foot but are useful when combined with other topical antifungal drugs. Application of solutions of aluminum salts merely shifts the disease process back to the simple dry type of athlete's foot, which can then be controlled with other agents such as tolnaftate or an imidazole.

Aluminum acetate for use in tinea pedis generally is diluted with about 10–40 parts of water. Depending on the clinical situation, the whole foot may be immersed in the solution for 20 minutes up to 3 times a day (every 6–8 hours), or the solution may be applied to the affected area in the form of a wet dressing.

For patient convenience, aluminum acetate solution (Burow's solution) or modified Burow's solution (which includes dextrin, polyethylene glycol, and sodium bicarbonate as inactive ingredients) is available for immediate use or as products formulated to be dissolved in water (powder packets, powder, effervescent tablets) (see [Chapter 35](#)). For preparation of packet-ready products, 1–3 packets are dissolved in 16 ounces of water.

Aqueous solutions of 20%–30% aluminum chloride have been the most beneficial for management of the wet, soggy type of athlete's foot.⁷ Twice-daily applications generally are used until the signs and symptoms (odor, wetness, whiteness) abate. After that, once-daily applications may be sufficient for control of symptoms. In hot, humid weather, the original condition may return within 7–10 days after the applications are stopped.

Pharmacotherapeutic Comparison

All of the topical antifungals approved for treating cutaneous fungal infections

have demonstrated effectiveness.^{28,29} A systematic Cochrane review of the data on tinea cruris and tinea corporis treatment found no superiority of one class over another; most evidence was of low quality, however, and clinical outcomes could be pooled only for terbinafine.²⁹ The allure of butenafine hydrochloride and terbinafine hydrochloride is their ability to cure athlete's foot in some patients after 1 week. A randomized trial of butenafine and clotrimazole for tinea cruris and tinea corporis showed butenafine to produce higher rates of clinical and mycologic cure at the end of week 1, yet no significance difference at 4 and 8 weeks of treatment.³⁰

A systematic review and meta-analysis for the treatment of any dermatomycosis also supports the effectiveness of azoles, allylamines, and other antifungals compared with placebo.³¹ There was no significant difference in efficacy rate between azoles and allylamines, but cure outcomes appeared to be sustained with allylamines (e.g., terbinafine) compared with azoles. No differences were found in safety or tolerability for any of the antifungal classes.³¹

Product Selection Guidelines

Before recommending a nonprescription product, the health care provider should review the patient's medical history for comorbid conditions affecting management. With coexisting diabetes, for example, good control of blood glucose levels is necessary because increased glucose in perspiration may promote fungal growth. Patients with allergic dermatitis often have a history of asthma, hay fever, or atopic dermatitis, so they may be extremely sensitive to many oral and topical agents. Acquiring a thorough medical history may aid in distinguishing a tinea infection from atopic dermatitis and may avoid the recommendation of a product that might cause further skin irritation.

Cutaneous antifungals are available as ointments, creams, powders, and aerosols ([Table 42-2](#)). Creams or solutions are the most efficient and effective dosage forms for delivery of the active ingredient to the epidermis and are preferable for dry and scaly tinea pedis. However, gels and sprays are preferred for macerated, erosive interdigital tinea pedis.²³

Patient adherence is influenced by product selection. Accordingly, the provider should recommend a drug and dosage form that are likely to cause the least interference with daily habits and activities, without sacrificing efficacy. For

example, older patients may require a preparation that is easy to use. Obese patients, in whom excessive sweating may contribute to the disease, should sprinkle talcum powder on the feet and in the shoes as adjunctive therapy to keep the feet dry.

In addition, product line extensions that carry the same brand name do not necessarily have the same active ingredient(s). For example, the cream and solution formulations of Lotrimin AF contain clotrimazole 1%, whereas the topical spray and powder formulations contain miconazole nitrate 2%. Lotrimin Ultra, the most recent line extension, contains butenafine hydrochloride. Similarly, Desenex spray liquid, spray powder, and spray powder formulations contain miconazole nitrate 2%, whereas these products formerly contained undecylenic acid.

Special Populations

Although topical medications are considered safer in pregnancy owing to limited systemic absorption, their safety profile must still be appropriately assessed. In a review of the relevant data for available nonprescription products used as topical antifungals in human and animal studies, clotrimazole and miconazole were preferred over butenafine and terbinafine.³² Please refer to the Preface for a detailed explanation of the pregnancy data.

Complementary Therapies

Bitter orange, tea tree oil, and garlic have been used with some success in the management of fungal skin infections, with few or no adverse effects. None of the studies that examined these ingredients included more than 60 patients, but the results suggest that further investigation of each complementary therapy is warranted.^{33–39}

Bitter orange has the least evidence of safety and efficacy. However, in one controlled trial, topical application of 25% oil of bitter orange 3 times daily demonstrated benefit in 1–4 weeks in most patients with tinea corporis, tinea cruris, or tinea pedis. The only reported side effect was mild, local irritation.³³

Investigations into the efficacy of tea tree oil for tinea pedis have yielded mixed results. In one study that compared tolnaftate 1% cream with tea tree oil 10% cream, both agents were equally effective in relieving the associated scaling, inflammation, itching, and burning, but neither agent was more effective than

placebo in achieving mycologic cure.³⁴ Results of two other studies suggest that tea tree oil 25% and 50% appear to result in both symptomatic and mycologic cure of tinea pedis. However, the mycologic cure rates were inferior to those for butenafine and clotrimazole.^{35,36}

Research relative to the efficacy of topical garlic for the management of tinea infections has yielded positive results. For example, application of a garlic gel containing 0.6% ajoene (a constituent of garlic believed to have antifungal activity) was demonstrated to be as effective as terbinafine 1% cream in a study of subjects with either tinea corporis or tinea cruris.³⁷ In another study comprising 34 patients, the use of ajoene 0.4% as a cream resulted in clinical and mycologic cure in all subjects after 2 weeks of use.³⁸ In a subsequent study, ajoene 1% cream was shown to produce a higher mycologic cure rate compared with ajoene 0.6% and terbinafine 1% creams.³⁹

Algorithm: Fungal Skin Infections

FIGURE 42–1 Self-care for fungal skin infections.

Assessment of Fungal Skin Infections: A Case-Based Approach

Fungal skin infections must be differentiated from bacterial skin infections and noninfectious dermatitis. If possible, the health care provider should examine the affected area to determine whether the clinical presentation is typical of a fungal infection ([Table 42–1](#)).⁴⁰ The only true diagnostic confirmation of a fungal infection is obtained by clinical laboratory evaluation of tissue scrapings from the affected area.

At the initial patient interview, assessment should be directed at identifying specific characteristics of the skin condition to determine symptoms, extent of disease, previous adherence to medication regimens, and any compounding disorders (e.g., diabetes, obesity) that may contribute to difficulties in management. Patients with diabetes, for example, may present with a mixed dermatophytid and candidal infection. In general, inspection of the affected

area is appropriate if privacy and sanitary conditions allow. Inspection is especially important for assessment in patients with diabetes.

Cases 42-1 and 42-2 are examples of the assessment of two different patients with a fungal skin infection.

The most common symptom associated with cutaneous fungal infections is pruritus. However, if fissures are present, particularly between the toes, the patient also may experience painful burning and stinging. If the affected area is abraded, denuded, or inflamed, weeping or oozing may occur, in addition to pain. Some patients may merely remark on the bothersome scaling of dry skin, particularly if the infection involves the soles of the feet. In other instances, small vesicular lesions may combine to form a larger bullous eruption marked by pain and irritation, or the only manifestations may be brittleness and discoloration of a hypertrophied nail.⁵

It is important to distinguish a tinea infection from diseases with similar symptomatology, such as bacterial infection, irritant contact dermatitis, allergic contact dermatitis, and atopic dermatitis. Accordingly, the typical clinical manifestations in these disorders are briefly reviewed here. In children, peridigital dermatitis or atopic dermatitis is more common than tinea pedis. Shoe dermatitis is perhaps the most common form of allergic contact dermatitis from clothing, so the assessment should ascertain the type of footwear worn by the patient, including recent footwear changes. The increased use of rubber and adhesives in footwear has paralleled the increase in reports of shoe dermatitis in the dermatologic and podiatric literature. Contact allergy to accelerators (the chemical compounds used to speed the processing of rubber used in sponge-rubber insoles for tennis shoes) also has been reported.⁴¹ In addition to accelerators, antioxidants have been implicated as major chemical allergens, and various phenolic resins used in adhesives also are troublesome. The patient usually is unaware that the footwear may be the cause of the problem.

Hyperhidrosis of interdigital spaces and of the sole of the foot is common, as is infection of the toe interspaces by gram-negative bacteria. In hyperhidrosis, tender vesicles cover the sole of the foot and toes, and these areas may be quite painful. The skin generally turns white, erodes, and becomes macerated. This condition is accompanied by a foul foot odor. A soggy wetness of the toe webs and the immediately adjacent skin characterizes infection by gram-negative bacteria; the affected tissue feels damp and softened to touch. The

last toe web (adjacent to the little toe) is the most common area of primary or initial involvement because it is deeper and extends more proximally than the web between the other toes. Other factors such as an abundance of exocrine sweat glands, a semiocclusive anatomic site, and the added occlusion provided by footwear contribute to development of the disease at this site. The provider must be careful not to confuse this condition with soft corns, which also appear between the fourth and fifth toes.

Case 42-1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient presents to the pharmacy with redness in the shape of eyeglasses on her nose and around both eyes. Scaling and weeping vesicles on both eyelids extend upward to both eyebrows. The patient has an open sore on the bridge of her nose that she admits she caused by scratching the area. She also complains of intense itching. Her symptoms began about a month ago, right after she started to swim competitively at school. She denies changes in swimming equipment, including goggles.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	She says that the itching is worse after she removes her swim goggles.
c. Description of the patient's efforts to relieve the symptoms	She has tried hydrocortisone ointment with no relief.
d. Patient's identity	Sara Lansbury

Relevant Evaluation Criteria	Scenario/Model Outcome
e. Patient's age, gender, height, and weight	21 years, female, 5 ft 6 in., 128 lb
f. Patient's occupation	College student who participates in competitive swimming
g. Patient's dietary habits	Patient is a vegetarian.
h. Patient's sleep habits	Number of hours that patient sleeps each night varies.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	<i>Seasonal allergies:</i> Claritin D (loratadine/pseudoephedrine) in the spring and fall
j. Allergies	Ragweed and maple trees
k. History of other adverse reactions to medications	None
l. Other (describe) -----	Patient has a history of ringworm during swim season.
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s) (Table 42-1).	Patient is suffering from inflammation, weeping, denudation, and intense itching on her face, secondary to ringworm.
3. Identify exclusions for self-treatment (Figure 42-1).	Severe symptoms, eye involvement, eyebrow involvement
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and	Options include (1) Refer the patient to a dermatologist or other appropriate health care provider. (2) Recommend self-care with a nonprescription antifungal and nondrug measures.

Relevant Evaluation Criteria	Scenario/Model Outcome
share this information with the patient or caregiver.	(3) Recommend self-care until patient can see an appropriate PCP. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Patient should consult a dermatologist or other knowledgeable health care provider.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"You should consult an appropriate health care provider for treatment."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"This option is best because your skin problem is severe and is affecting areas near your eyes. You will need an oral medication that is available only by prescription to treat your condition."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	"Make sure you dry off well after swimming, and allow your face to air dry completely. Do not share towels or other sports equipment."
Solicit follow-up questions from the patient or caregiver.	"One of my teammates said that I should suffocate the ringworms by applying clear nail polish on the itchy spots. Does this really work?"
Answer the patient's or	"Ringworm is not actually caused by worms. It is caused by a

Relevant Evaluation Criteria	Scenario/Model Outcome
caregiver's questions.	fungus that lives in the superficial skin layers. Nail polish will have no effect on your symptoms. It can, however, cause severe irritation if you get it in your eyes."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Ms. Lansbury in 1-2 days to ensure that she made an appointment and sought medical care.

Case 42-2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient is seeking a pharmacist's recommendation for intense pruritus (itching) and a red, scaly rash on and between the third, fourth, and fifth toes of each foot. He states that the problem began a week ago, soon after he began his summer job at a lawn maintenance service.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	The patient states that the itching is worse after he gets home from work in the evening.
c. Description of the patient's efforts to relieve the symptoms	The patient has not tried anything other than scratching the affected area when the itching becomes "unbearable."
d. Patient's identity	Robert Grees
e. Patient's age, gender, height,	17 years, male, 5 ft 11 in., 175 lb

Relevant Evaluation Criteria	Scenario/Model Outcome
and weight	
f. Patient's occupation	High school senior with full-time summer job as lawn maintenance worker
g. Patient's dietary habits	Eats fast food for breakfast and lunch and a frozen prepared meal for dinner.
h. Patient's sleep habits	He sleeps 6–7 hours nightly.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	None
j. Allergies	None
k. History of other adverse reactions to medications	None
l. Other (describe) _____	N/A
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s) (Table 42–1).	The scaly red rash and itching are manifestations of athlete's foot. The patient likely contracted the condition while working outside in the summer heat and humidity.
3. Identify exclusions for self-treatment (Figure 42–1).	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer Mr. Grees to an appropriate health care provider. (2) Recommend self-care with a nonprescription antifungal and nondrug measures. (3) Recommend self-care until Mr. Grees can see an appropriate health care provider.

Relevant Evaluation Criteria	Scenario/Model Outcome
	(4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Mr. Grees should use a nonprescription antifungal medication and nondrug measures to treat this condition.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Regular use of any of the commercially available nonprescription antifungals in any dosage form should alleviate the problem. However, for the medication to be optimally effective, you will have to keep the affected areas clean and dry."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Athlete's foot can be effectively managed with nonprescription antifungals and nondrug measures (if the area is kept clean and dry) as long as there is no evidence of secondary infection or preexisting medical conditions that would preclude self-treatment, as in your case. Sprays and powders are less effective because they often are not rubbed into the skin."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
a. Appropriate dose and frequency of administration	See the box "Patient Education for Fungal Skin Infections."
b. Maximum number of days the therapy should be employed	See the box "Patient Education for Fungal Skin Infections."
c. Product administration procedures	See the box "Patient Education for Fungal Skin Infections."
d. Expected time to onset of relief	"Itching may be relieved somewhat within a few days, but eradication of the causative microorganism may take up

Relevant Evaluation Criteria	Scenario/Model Outcome
	to 4–6 weeks, depending on the agent used.”
e. Degree of relief that can be reasonably expected	“Athlete’s foot can be cured if you use the antifungal and nondrug measures properly.”
f. Most common adverse effects	See the box “Patient Education for Fungal Skin Infections.”
g. Adverse effects that warrant medical intervention should they occur	See the box “Patient Education for Fungal Skin Infections.”
h. Patient options in the event that condition worsens or persists	See the box “Patient Education for Fungal Skin Infections.”
i. Product storage requirements	“Store in a cool, dry place out of children’s reach.”
j. Specific nondrug measures	See the box “Patient Education for Fungal Skin Infections.”
Solicit follow-up questions from the patient or caregiver.	“Why do I have this? I am not an athlete.”
Answer the patient’s or caregiver’s questions.	“Your feet are sweating more than usual now because you are working in summer temperatures for prolonged periods during the day. As a result, the skin of your feet remains damp until you remove your shoes and socks after work. Moisture helps the fungus that causes athlete’s foot to thrive.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Ask Mr. Grees to call to update you on his response to your recommendations 1 week after initiating treatment. Or you could call him in a week to evaluate the outcome.

Key: N/A = Not applicable.

Patient Counseling for Fungal Skin Infections

The proper application technique for topical antifungals and the required duration of therapy should be emphasized in patient counseling, to prevent over- or undermedicating. The patient should be directed to apply the medication regularly throughout a complete course of therapy. The approved indications for the products also should be discussed, because some fungal infections are not amenable to management with nonprescription products, and marketing ploys (e.g., pictures) may be misleading. Information on measures that will help to control or eradicate the infection and that will minimize the likelihood of recurrent infections also may be provided. Such measures may include proper care of the infected skin site, use of appropriate laundry techniques and products, limiting wear of occlusive clothing, and avoidance of habits or behavior that may lead to recurring infections. A critical component of patient counseling is identification of conditions that warrant consultation with an appropriate health care provider for further evaluation and treatment (e.g., the development of a secondary bacterial infection). The box “Patient Education for Fungal Skin Infections” summarizes information to provide in patient counseling.

Evaluation of Patient Outcomes for Fungal Skin Infections

In general, the patient should begin to experience some relief of the itching, scaling, and/or inflammation within 1 week. If clinical improvement is seen within this time frame, continuing treatment for 1–4 weeks (depending on the type of tinea infection and medication being used) should be recommended. If the affected skin has not improved or the disorder has worsened, referral to a dermatologist or other knowledgeable health care provider for more aggressive therapy is appropriate. Recurrent skin infections may be a sign of undiagnosed diabetes, immunodeficiency, or another organic problem that requires medical evaluation.

Patient Education for Fungal Skin Infections

The objectives of self-treatment are (1) to relieve itching, burning, and

other discomfort; (2) to inhibit the growth of fungi and cure the disorder; and (3) to prevent recurrences of the infection. For most patients, carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

Nondrug Measures

- To prevent spreading the infection to other parts of the body, either use a separate towel to dry the affected area or dry the affected area last.
- Do not share towels, clothing, or other personal articles with household members, especially when an infection is present.
- Launder contaminated towels and clothing in hot water and then dry them on a hot dryer setting to prevent spreading the infection.
- Cleanse skin daily with soap and water, and thoroughly pat dry to remove oils and other substances that promote growth of fungi.
- If possible, do not wear clothing or shoes that cause the skin to stay wet. Wool and certain synthetic fabrics prevent optimal air circulation.
- If needed, allow shoes to dry thoroughly before wearing them again. Dust shoes with medicated or nonmedicated foot powder to help keep them dry.
- If needed, place odor-controlling insoles in casual or athletic shoes. These insoles also provide some additional support and cushioning for the feet. Change insoles routinely every 3–4 months or more often if their condition warrants. Take care that the shoe fit is not compromised by presence of the insoles.
- As with all topical medications, discontinue the use of an antifungal if irritation, sensitization, or worsening of the skin condition occurs.
- Avoid contact with people who have fungal infections. Wear protective footwear (e.g., rubber or wooden sandals) in areas of family or public use, such as home bathrooms or community showers.

Nonprescription Medications

- Ask a health care provider for assistance in picking the appropriate

antifungal agent and dosage form for your infection.

- Available agents include undecylenic acid, butenafine, clotrimazole, miconazole nitrate, terbinafine, and tolnaftate.
- It usually takes 2–4 weeks to cure tinea infections. Some cases may require 4–6 weeks of treatment.
- Apply the antifungal to the clean, dry affected area as directed (in the morning or evening if once daily, or both times if twice daily). Massage the medication into the area. Note that creams and solutions are easier to work into the skin.
- Avoid getting the product in your eyes.
- Wash hands thoroughly with soap and water before and after applying the product.
- Topical antifungals themselves may cause itching, redness, and irritation.
- Tolnaftate may sting slightly upon application.
- When the medication is to be applied to pressure areas of the foot, where the horny skin layer is thicker, apply a keratolytic agent (e.g., salicylic acid) to the affected area first to help the antifungal penetrate the skin.
- If oozing lesions are present, apply aluminum acetate solution to the area before applying the antifungal:
 - Soak the area in an aluminum acetate solution for 15–30 minutes up to 3 times a day (every 6–8 hours), or apply the solution to the affected area in the form of a wet dressing.
 - Note that aluminum acetate solution (Burow's solution) or modified Burow's solution is available for immediate use or can be prepared from various products formulated to be dissolved in water (powder packets, powder, and effervescent tablets).
 - Avoid getting the product in your eyes.
 - To avoid skin damage, use the solution for no more than 1 week. Discontinue use of the solution if inflammatory lesions appear or worsen.
- For the wet, soggy type of athlete's foot, apply aluminum acetate solution as a topical agent or as foot soaks before applying the antifungal:

- Soak feet with aluminum acetate solution twice daily until the odor, wetness, and whiteness are gone. After that, soak once daily to control the symptoms.
 - If deep fissures are present, use a more dilute solution of aluminum acetate for initial treatment.
 - A solution of 30% aluminum chloride twice daily can be applied for treating athlete's foot.
- Antifungal medication can be applied immediately after soaking once the area has dried.

When to Seek Medical Attention

- Discontinue use of the product and contact an appropriate health care provider if itching or swelling occurs, or if the infection worsens.
- Consult a primary care provider if the infection worsens or persists beyond the recommended length of therapy.
- Seek medical attention if the infection worsens, fails to respond to treatment within 1 week, or persists beyond the recommended duration of therapy.

Key Points for Fungal Skin Infections

- Tinea corporis, tinea cruris, and tinea pedis can be treated with nonprescription drugs. Clotrimazole, miconazole nitrate, terbinafine hydrochloride, butenafine hydrochloride, tolnaftate, and undecylenic acid are efficacious for this purpose.
- The effectiveness of topical antifungals will be limited unless the patient eliminates other predisposing factors to tinea infections.
- These drugs are effective in all available delivery vehicles, but the powder forms should be reserved only for extremely mild conditions or as adjunctive therapy.

- Because solutions and creams can spread beyond the affected area, they should be used sparingly.
- When recommended for suspected or actual dermatophytosis, these topical antifungals should be used once or twice daily (morning and night), depending on the indication. Treatment should be continued for 1–4 weeks, depending on the symptoms and the type of fungal infection. After that time, the patient and/or the provider should evaluate the effectiveness of the therapy.
- To minimize nonadherence, the provider should advise patients that alleviation of symptoms will not occur overnight. Patients also should be cautioned that frequent recurrence of any of these problems is an indication for seeking consultation with their primary care provider or a dermatologist.
- Dermatophytoses in immunocompromised patients and those with diabetes or circulatory problems require medical management.
- The only antifungal currently approved for prevention of athlete's foot is tolnaftate.

Chapter 43: Warts

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Warts, or verrucae, are a common skin disorder caused by the human papillomavirus (HPV), of which various pathogenic subtypes are recognized.¹⁻¹² Approximately 7%–10% of the general population has warts, with common warts accounting for approximately 70% of the cases.¹⁻⁴ Warts occur more frequently in children and adolescents than in infants and adults, with the peak incidence among 12- to 16-year-olds.^{1,2,5} Warts are considered a benign condition, which often resolves without treatment. Approximately 23% of warts regress within 2 months and 65%–78% within 2 years.^{1,6,11} This chapter discusses self-treatment for nongenital warts—specifically, common and plantar warts, found typically on the hands and feet, respectively.

Pathophysiology of Warts

HPVs are double-stranded DNA viruses.^{1-6,8} More than 150 related viruses and 200 subgroups have been identified.² HPV infection occurs via person-to-person contact, autoinoculation, or transmission on fomites (contaminated objects or surfaces).^{1,3,7} Warts may affect skin and mucous membranes anywhere on the body. HPV infection is limited to the epidermal tissues and does not spread systemically. When minor skin abrasions are present, HPV may enter the epidermal layer and infect the basal keratinocytes.¹ The incubation period may be long (e.g., months).^{2,11} The manifestation of warts may depend on the immune response of the infected person. How quickly warts are cleared is influenced by factors such as viral type, patient immune status, and the extent of involvement and length of time the warts have been present.¹ Several risk factors for the development of warts are recognized, including existing or previous warts; immunocompromised status; presence of a chronic skin condition; going barefoot, especially on wet surfaces; use of swimming pools and public showers; employment in a meat-handling facility; and biting the nails.^{1-3,5,9}

Clinical Presentation of Warts

The appearance, size, shape, and response to treatment of individual warts vary by HPV subtype and the specific location of the lesion on the body.^{1,3,9} Although different types of HPV are not found exclusively in specific areas of the body, HPV-2, HPV-4, HPV-27, and HPV-57 constitute the most common cause of warts on the hands, and HPV-1 is the most common cause of warts on the feet.^{1,7,12}

Table 43–1 describes the categories of warts.

TABLE 43–1 Types of Nongenital Warts				
Wart Type	Common Location	Population(s) Commonly Affected	Characteristics	Self-Treatable
Common (verruca vulgaris)	Hands	Children and adolescents	Skin-colored or brown, dome-shaped, hyperkeratotic papules with a rough surface	Yes
Flat (verruca plana)	Face	Children	Smooth, flat-topped, yellow-brown papules; zcommon in children but rare in adults	No
Plantar (verruca plantaris)	Feet	Adolescents and young adults	Skin-colored, flat, callus-like, hyperkeratotic lesions with disruption of normal skin markings; located on the feet	Yes
Mosaic	Feet	Adolescents and young adults	Multiple, closely grouped plantar warts	No
Periungual	Nails	Persons who bite their nails	Thickened, fissured, cauliflower-textured skin around the nail plate	No
Filiform	Face		Flesh-colored, rapidly growing, with threadlike projections	No

Source: [References 1, 2, 5, and 9.](#)

Common warts are skin-colored or brown, hyperkeratotic, dome-shaped

papules with a rough-looking, often cauliflower-textured surface; they frequently occur on the hands (see [Color Plates](#), photograph 33).^{1,2} Common warts often are painless.² Plantar warts are skin-colored callus-like lesions that occur on the feet (see [Color Plates](#), photograph 34).² Because the underside of these lesions extends deeply into the epidermis, with an external conformation of sloping sides and a central depression, plantar warts may be painful, especially if they occur in a weight-bearing location.¹ When tightly clustered, multiple plantar warts may appear as one large wart. In this presentation, the lesion is called a mosaic wart.^{1,2}

Plantar warts can be confused with corns or calluses.¹ If there is any question about whether the lesion is a wart, the patient should be referred to an appropriate health care provider for evaluation and treatment. To distinguish plantar warts from calluses, the provider may remove the outer keratinous layer of the lesion. When the surface layer is removed, the wart exhibits pinpoint bleeding, which looks like small dark red or black dots. The bleeding is from thrombosed capillaries within the wart.¹

Plantar warts also can be confused with malignant growths.⁶ The latter usually are very painful and discolored, and they bleed and grow quickly.⁷ Patients with lesions displaying these characteristics should be referred for medical evaluation and treatment.

Treatment of Warts

No single treatment regimen is universally effective in the treatment of warts.^{1,4,9} Although several treatment options are available for relief of symptoms associated with warts and for their removal, none cure the HPV infection.^{1,4,9} High-quality evidence for the efficacy of most wart treatments is limited, and a placebo effect cannot be ruled out.^{1,4,7}

Because many warts will resolve without treatment, one management option is a wait-and-see approach. However, many patients seek treatment because of the pain, cosmetic appearance, and social stigma associated with warts or because of concern about transmitting warts to others. The decision to treat a wart is based on the patient's desire for treatment; the presence of pain or bleeding, disabling, and/or disfiguring lesions, or large or multiple lesions; the desire to prevent transmission of the warts; and the absence of any exclusions

for self-care such as immuno compromised status.^{4,8} Warts often recur after treatment. With recurrent or persistent warts, a combination of treatments may be required.¹

Treatment Goals

The goals for treatment of warts are (1) to eliminate associated signs and symptoms, (2) to remove the lesion without scarring, (3) to prevent recurrence of the warts, and (4) to prevent spread of HPV through autoinoculation or transmission to others.⁸

General Treatment Approach

Determining the optimal treatment for a patient with warts depends on a number of factors, including the patient's age; the type, number, size, location, and duration of the lesions; the patient's immune status; the cost of therapy; access to therapies; adverse effects; and treatment preference.^{1,4}

Although approximately 70% of warts will resolve after 2 years, even without treatment, only 46% of affected persons will remain wart-free.⁶ Warts are less likely to resolve spontaneously in adults, immunocompromised patients, and patients with other warts that persist despite treatment.¹ A wait-and-see approach allows the continued spread of warts through autoinoculation and transmission to others.^{4,6,7} Accordingly, prompt patient education regarding the cause of warts and ways to prevent their transmission to others is a key part of the treatment plan.

Figure 43–1 outlines the treatment of warts and lists exclusions for self-treatment. With multiple warts, warts in any area other than the hands and feet, warts on the fingernails, large warts, and/or painful warts, further medical evaluation is warranted to determine whether the lesions may be caused by a more serious condition. In patients with poor circulation or decreased skin sensitivity (e.g., patients with diabetes or peripheral vascular disease), self-treatment for warts is contraindicated because of the potential for injury.

Nonpharmacologic Therapy

Nonpharmacologic therapies focus mainly on preventing the spread of HPV. To prevent further development of warts from autoinoculation, patients should

be instructed to avoid cutting, shaving, or picking at warts; to wash hands before and after treating or touching warts; and to use a designated towel to dry wart-affected areas, with care taken to avoid its contact with the skin elsewhere. To prevent transmission of the virus to others, patients also should be instructed to avoid sharing towels, razors, socks, shoes, and so forth; to keep the wart covered; and to not walk barefoot, especially in bathrooms or in public places. For patients experiencing discomfort from plantar warts, padding such as lamb’s wool or moleskin may be used over the pressure points to help relieve the discomfort.

Pharmacologic Therapy

Salicylic Acid

Salicylic acid is a keratolytic agent available in several formulations for use in self-treatment for common and plantar warts: salicylic acid 17% liquid and gel and salicylic acid 40% plaster, pads, strips, and sticks.^{2,13} **Table 43–2** lists selected products that contain salicylic acid. Salicylic acid concentrations of 17% generally are used for common warts, and higher concentrations (i.e., 40%) are used for plantar warts.⁹

TABLE 43–2 Selected Self-Care Products for Warts	
Trade Name	Primary Ingredient(s)
Compound W One Step Pads	Salicylic acid 40%
Curad Medioplast Pads	Salicylic acid 40%
Dr. Scholl’s Clear Away One Step Clear Strips	Salicylic acid 40%
DuoFilm Wart Remover Patch	Salicylic acid 40%
WartStick	Salicylic acid 40%
Compound W Fast Acting Wart Removal Gel	Salicylic acid 17%
Compound W Fast Acting Wart Removal Liquid	Salicylic acid 17%
Dr. Scholl’s Clear Away Fast-Acting Liquid	Salicylic acid 17%
DuoFilm Liquid Wart Remover	Salicylic acid 17%

Trade Name	Primary Ingredient(s)
Compound W Freeze Off Wart Removal System	<i>Cryotherapy:</i> Dimethyl ether; propane
Compound W Freeze Off Advanced	<i>Cryotherapy:</i> Dimethyl ether; propane
Dr. Scholl's Freeze Away Wart Remover	<i>Cryotherapy:</i> Dimethyl ether; propane
Wartner Cryogenic Wart Removal System	<i>Cryotherapy:</i> Dimethyl ether; propane
Compound W NitroFreeze	<i>Cryotherapy:</i> Nitrous oxide

Source: References 19 and 20; and U.S. News & World Report and Pharmacy Times. Health: wart removers. Available at: <http://health.usnews.com/health-products/top-rec-wart-removers-146>. Accessed May 8, 2019.

Salicylic acid slowly destroys the virus-infected cells. It also may induce an immune response secondary to mild irritation.^{1,3-5,9} The U.S. Food and Drug Administration (FDA) recommends that use of salicylic acid for self-treatment for warts be restricted to common and plantar warts.¹³ Self-treatment is not recommended for other types of warts because of the difficulty in accurately recognizing and treating warts without the oversight of a dermatologist or other experienced clinician. Patients with painful plantar warts and lesions that are not easily recognizable as common or plantar warts require further medical evaluation.

The advantages of topical nonprescription products that contain salicylic acid include low cost, ready availability, few adverse effects if used as directed, and reasonable effectiveness.^{1,3,5} Compared with placebo, salicylic acid is more effective in treating warts on both the hands and feet, but it may be more effective for warts on the hands than those on the feet.⁵ Disadvantages include the need for consistent, frequent application of the product 1–2 times daily; the potential for damage to healthy skin surrounding the wart; and the duration of treatment needed to achieve a therapeutic response.^{1,3,5,9} Adverse effects include skin irritation and the potential for systemic toxicity.^{1,3,9}

In most instances, warts will begin to decrease in size within a couple of weeks of treatment with salicylic acid. Self-treatment for common and plantar warts

should not continue past 12 weeks. Patients with warts that do not completely resolve after 12 weeks should be referred for further medical evaluation.

Table 43–3 provides guidelines for using salicylic acid products.^{14–16}

TABLE 43–3 Guidelines for Treating Warts With Selected Salicylic Acid Products	
General Guidelines	• Wash hands before and after use. • Before treatment, soak the affected area in warm water for 5 minutes. • Wash and dry the affected area thoroughly.
Salicylic Acid 40% Plasters/Pads/Strips/Sticks¹⁴	• Trim a plaster to fit the wart, apply plaster, and cover with an occlusive tape; apply disc of appropriate size to wart and cover with pad; apply strip to wart, making sure the disc in the strip does not touch healthy tissue; or apply stick to wart, making sure the stick is not on healthy tissue, and bandage or cover. • Remove plaster/pad/strip/stick after 48 hours. • Repeat procedure every 48 hours as needed until the wart resolves. These products may be used for up to 12 weeks.
Salicylic Acid 17% Liquid/Gel^{15,16}	• Apply 1 drop at a time to cover the wart. Protect adjacent healthy skin from coming into contact with the gel. • Let solution dry completely. • Cover wart with self-adhesive discs or an occlusive tape. • Repeat procedure 1–2 times a day until the wart resolves. This product may be used for up to 12 weeks.

Cryotherapy

Cryotherapy with liquid nitrogen and other agents has been used for many years for treatment of warts in the office setting.⁶ With this modality, destruction of the lesion is accomplished by freezing the wart tissue.^{6,9} Liquid nitrogen can reach temperatures of approximately -196°C (-385°F).^{3,7} As temperatures decrease to -5°C to -15°C (-41°F to -59°F), extracellular ice crystals form.⁶ At -40°C (-104°F) and below, intracellular ice crystals form.⁶ Freezing of tissue creates localized microthrombi, with consequent ischemic necrosis and destruction of the HPV-infected keratinocytes.⁶ The freezing also

causes local inflammation that may clear the wart through a cell-mediated response.^{1,4}

FDA has approved nonprescription products that contain either nitrous oxide (NO) or a mixture of dimethyl ether and propane (DMEP) for self-treatment for common and plantar warts. Although neither NO nor DMEP can reach temperatures as low as the liquid nitrogen used in the office setting, both NO and DMEP can reach temperatures cold enough for destruction of warts by freezing.^{1,3,17} Nonprescription cryotherapy products have similar, but product-specific, directions for preparing the applicator. **Table 43–4** provides guidelines for using cryotherapy products.^{18–20} The cryotherapy preparation is applied directly to the wart. Patients must follow the directions carefully to avoid damaging the healthy skin surrounding the wart. A blister will form under the wart, and if the treatment is effective, after about 10 days the wart will fall off. Applicators must not be used more than once, to avoid reinfecting the tissue or spreading the virus to others.

TABLE 43–4 Guidelines for Treating Warts With Cryotherapy Products^{19,20}

General Guidelines

- Wash hands before and after use.
- Before treatment, soak the affected area in warm water for 5 minutes.
- Wash and dry the affected area thoroughly.
- May use a file or pumice stone to lightly abrade the surface of plantar warts.
- Do not hold the cryotherapy product canister close to the face, body, or clothing.
- These products are flammable. Do not use near heat sources.
- Application:
 - Prepare the device (refer to product-specific instructions).
 - Activate the device (refer to product-specific instructions).
 - Apply to the wart until a “halo” appears around the wart (refer to instructions).
 - Approximately 20 seconds for common warts
 - Approximately 40 seconds for plantar warts
- Discard single-use applicators after one use.
- Repeat after 2 weeks if needed. This product may be used for up to 3 treatments.

With regard to success in treatment of both common and plantar warts, cryotherapy is no more effective than salicylic acid or placebo.^{3,5,9} One study found that cryotherapy may be more effective than salicylic acid for warts on

the hands but not on the feet.²¹ The use of two freeze–thaw cycles, instead of one, during a cryotherapy treatment may improve the clearance of plantar warts, but this approach has not been shown to improve clearance of common warts on the hands.^{1,3,11} However, nonprescription cryotherapy products are not approved to be used with two freeze-thaw cycles during a treatment. Aggressive cryotherapy treatments are more effective (52%) than gentle treatments (31%) but are associated with an increased incidence of adverse effects.^{1,3,5,9} Treating the wart every 2–3 weeks with cryotherapy yields the best results.^{5,11}

The advantages of nonprescription cryotherapy products include their ready availability and lower cost, compared with the liquid nitrogen used in the clinician’s office; in some cases, even a single treatment may be sufficient to clear the wart. Disadvantages of cryotherapy relative to salicylic acid treatments include associated pain and the potential for damage to healthy skin surrounding the wart; also, self-treatments may not be as effective as the liquid nitrogen used in the office setting. Potential adverse effects include blistering, scarring, hypo- or hyperpigmentation, and tendon or nerve damage with aggressive therapy.^{1,3,9}

In some cases, warts will resolve after a single treatment with self-cryotherapy. Self-treatment for common and plantar warts may be repeated every 2 weeks if the wart does not resolve after the first treatment. However, treatments should not continue beyond a maximum of 3 sessions or for more than 12 weeks’ duration. If this regimen does not completely resolve the wart, the patient should be referred to an appropriate health care provider for evaluation and treatment.

Other Pharmacologic Therapies

Numerous prescription products, laser treatments, immunotherapies, and combinations of treatments are used to treat warts. Discussion of prescription products and procedures is outside the scope of this chapter. Only limited or inconsistent data are available for the effectiveness of products other than salicylic acid and cryotherapy for self-treatment for common and plantar warts.

Product Selection Guidelines in Special Populations

Several factors should be considered in selecting a wart removal product, including the patient's age and pregnancy or lactation status, as well as the presence of certain medical conditions. The specific product chosen also must be compatible with the patient's lifestyle and personal preferences.

Pregnancy

The potential effects of topical salicylic acid or cryotherapy products on an unborn child when used by an expectant mother for treatment of warts are unknown. Accordingly, products of either type should not be used for self-treatment during pregnancy. In such cases, the patient should be referred for medical evaluation and treatment.

Lactation

It is not known if topical salicylic acid passes into breast milk in sufficient amounts to harm the infant. How cryotherapy products will affect either mother or child in this setting has not been established. Products containing salicylic acid or cryotherapy-specific ingredients should therefore not be used for self-treatment for warts in nursing mothers. These patients should be referred to an appropriate health care provider for evaluation and treatment.

Children

Topical salicylic acid products should not be used for self-treatment for warts in children younger than 3 years because of the potential for systemic absorption and for epithelial damage in this patient population. Furthermore, salicylic acid-containing products should not be used in children or teenagers who have or are recovering from chickenpox or influenza-like symptoms because of the risk of Reye syndrome (see [Chapter 5](#) for further information). In addition, cryotherapy products should not be used for self-treatment for warts in children younger than 4 years. The specific effects of such products on the skin of young children have not been determined, but in this vulnerable age group, the potential to cause significant skin damage should not be overlooked.

Patients of Advanced Age

Both cryotherapy products and salicylic acid–based preparations may be used in persons of advanced age in a manner similar to that for younger adults. With application of such products, however, care should be taken to avoid the normal skin tissue around the wart, because older patients often have thinner, more friable skin at increased risk for injury.

Comorbid Conditions

Patients with diabetes or poor circulation should not use cryotherapy or salicylic acid–containing products because of the associated risk for delayed healing.

Dosage Form Considerations

The salicylic acid–containing products come in a variety of dosage forms that may appeal to specific patient preferences, such as colored pads for children to cover the wart or strips or pads that may be easier for some patients to apply than the liquid. Cryotherapy products may appeal more to patients who are looking for a product that requires minimal applications.

Complementary Therapies

Folklore

Numerous folk remedies for warts have been recommended. Most of these are based on anecdotal success, highlighting the probability that many warts resolve spontaneously without treatment.¹

Vitamin A

Retinoids such as vitamin A regulate epithelial cell differentiation and keratin expression. Vitamin A may interfere with HPV replication. One case report of use of topical vitamin A for recalcitrant hand warts in a 30-year-old woman found this agent to be effective in clearing the lesions.¹² The report noted that untreated warts on the opposite hand cleared without application of vitamin A, which may illustrate either a placebo effect or an unknown mechanism of action.¹²

Dietary Zinc

Deficiencies of zinc lead to decreased immunity.^{1,10} Dietary zinc is postulated to improve immune response and inhibit HPV replication.¹⁰ One placebo-controlled trial evaluated 10 mg/kg/day of zinc to treat recalcitrant warts. Complete clearance was reported in 35 of the 40 patients, or 87%, in the treatment group, versus no clearance in the placebo group.^{1,10}

Garlic (*Allium sativum*)

Garlic is thought to inhibit cellular proliferation of virus-infected cells.^{1,22} In a placebo-controlled trial, application of chloroform extracts of garlic resulted in complete resolution of warts in all 23 patients after 1–2 weeks, with no recurrence after 3–4 months.^{1,22}

Occlusion With Duct Tape

Occlusion with duct tape is an inexpensive, potentially less painful self-treatment for warts. The mechanism by which this approach clears warts is still unclear, but local irritation may cause stimulation of the patient's immune response.⁵

One randomized controlled study²³ compared duct tape occlusion with cryotherapy for the treatment of common warts. In the cryotherapy group, liquid nitrogen was applied to warts every 2–3 weeks, for a maximum of 6 treatments or until regression of the warts was achieved. In the occlusion therapy group, duct tape was applied to the wart, left in place for 6 days, removed on the evening of the sixth day, and replaced with a new piece of duct tape the next morning; this multistep procedure was repeated for up to 2 months or until the wart resolved. The treated warts regressed completely in 84.6% of the patients in the duct tape occlusion group and in 60% of the patients in the cryotherapy group.²³

Another randomized controlled trial yielded conflicting results. This trial compared use of moleskin overlaid with duct tape versus moleskin alone in occlusion therapy for warts. In both treatment groups, the wart was shaved; next, either a taped or untaped moleskin pad was applied for 6 of 7 days each week. The wart was then debrided with an emery board, and the taped or untaped pad was reapplied for an additional week. This procedure was

repeated for up to 2 months or until the wart resolved. At 6-month follow-up evaluation, patients were asked if the wart had recurred. The treatment groups demonstrated no difference in resolution or recurrence of the warts.^{5,24}

More evidence on the effectiveness of occlusion therapy with duct tape is needed. Duct tape occlusion may have a place in therapy for young children with warts or in combination with other treatments.¹

Algorithm: Warts

FIGURE 43–1 Self-care for warts. Key: DMEP = Dimethyl ether and propane; PVD = peripheral vascular disease; SA = salicylic acid.

Assessment of Warts: A Case-Based Approach

When a patient presents with a wartlike lesion, the health care provider should gather information from multiple sources to determine whether the lesion is suitable for self-treatment and whether available therapies are appropriate for that patient. Before a treatment plan is recommended, the provider should inspect the wart to accurately identify the lesion as a wart and to determine whether self-treatment is appropriate. The patient interview should include a current medication history to identify all prescription and nonprescription drugs with potential for adverse interactions and a health status review to disclose any concomitant medical conditions that constitute exclusions to self-care. The patient also should be asked about previous attempts to treat the lesion and whether any improvement was obtained with those attempts. Patient preferences for type of treatment may be used to help guide product selection.

Table 43–5 compares characteristics of warts, corns, calluses, and malignant growths. Cases 43–1 and 43–2 illustrate the assessment of two different patients with warts.

TABLE 43–5 Differentiation of Warts and Skin Disorders With Similar Presentation

Criterion	Warts	Corns	Calluses	Malignant Growth
Location	Any area of skin susceptible to the causative virus	Over bony prominences in the feet	Weight-bearing areas of the feet	Any area of the skin
Conformation/ clinical signs	Rough cauliflower-like appearance; plantar warts disrupt normal skin ridges	Raised, sharply demarcated, hyperkeratotic lesions with a central core	Raised, yellowish thickening of the skin; broad-based with diffuse borders; normal pattern of skin ridges	Bleeding; swelling; red, discolored, or multicolored and swollen
Pain symptoms	Usually not painful, but pain may occur if the wart is located in areas under constant pressure (e.g., soles of the feet)	Painful	Usually not painful, but pain may occur if the callus is located in an area where significant pressure may occur (e.g., soles of the feet)	Painful
Size/severity	Varies; may grow to approximately 1 inch in diameter	Varies; a few millimeters to 1 cm	Varies; a few millimeters to several centimeters	Varies; grows rapidly
Timing	Incubation period may be several months in duration; may progressively enlarge	Variable onset; may progressively enlarge	Variable onset; may progressively enlarge	Variable onset; grows rapidly
Cause	HPV infection of the epidermal layer	Friction	Friction, walking barefoot, structural foot problems	Mutations related to damaged DNA causing skin cells to grow unchecked
Modifying factors	Prevention of spread; treatment with salicylic acid or cryotherapy	Alleviation of causative factors; treatment	Alleviation of causative factors; treatment with salicylic acid	Surgical removal; prescription medications

Criterion	Warts	Corns	Calluses	Malignant Growth
		with salicylic acid		

Key: HPV = Human papillomavirus.

Patient Counseling for Warts

The health care provider has a crucial role in educating patients that warts are caused by HPV and are contagious. Consistent implementation of measures to prevent the spread of warts (see “Nonpharmacologic Therapy”) to other parts of the body or to other persons is a critical component of successful management. The differences between available products for wart removal, including their indications, contraindications, warnings, and precautions, also should be highlighted in discussions with the patient. The box “Patient Education for Warts” lists specific information to provide in patient counseling for use of either salicylic acid or cryotherapy products. If warts persist despite self-treatment for a maximum of 12 weeks of therapy, patients should be referred for medical evaluation and treatment.

Evaluation of Patient Outcomes for Warts

Salicylic acid may require up to 12 weeks of treatment to completely clear the wart. Patients should see some improvement in 1–2 weeks. Follow-up evaluation with the health care provider should occur after 4–6 weeks to assess progress in clearing the wart. If the wart does not appear to be resolved, the patient should be encouraged to continue treatment. If the wart has not cleared after 12 weeks, prescription therapies may be warranted, so the patient should be referred for further medical evaluation.

Cryotherapy may be repeated after 2 weeks for up to 12 weeks or 3 treatments. If the wart has not cleared after 12 weeks or 3 treatments, referral for medical evaluation and treatment is warranted.

Case 43–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient states that she has a rough spot on the bottom of her left big toe. She noticed it about 2 weeks ago. It is not painful. Even though it is small, she is self-conscious about it and embarrassed to go barefoot because of how she thinks it looks. The normal skin ridges are disrupted. No inflammation, bleeding, significant discoloration, or discharge from the lesion is evident.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	None that patient has identified
c. Description of the patient's efforts to relieve the symptoms	Patient has not yet tried anything to get rid of the lesion.
d. Patient's identity	Sage Justus
e. Patient's age, gender, height, and weight	18 years, female, 5 ft 4 in., 130 lb
f. Patient's occupation	College student who works weekends as a lifeguard at the local public pool
g. Patient's dietary	Ms. Justus follows a generally healthy diet.

Relevant Evaluation Criteria	Scenario/Model Outcome
habits	
h. Patient's sleep habits	6–8 hours of sleep a night
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	No medical conditions Medication(s): triphasic oral contraceptive daily; adult multivitamin daily
j. Allergies	None
k. History of other adverse reactions to medications	None
l. Other (describe) _____	Ms. Justus lives on campus in a dorm with a communal bathroom on each floor. She has one roommate.
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Ms. Justus appears to have a plantar wart. She most likely contracted it by walking barefoot at the pool or in the dorm showers.
3. Identify exclusions for self-treatment (Figure 43-1).	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health	Options include (1) Recommend self-care with a nonprescription wart removal product and nondrug measures. (2) Recommend self-care until the patient can consult a knowledgeable health care provider for evaluation and

Relevant Evaluation Criteria	Scenario/Model Outcome
care provider is required, and share this information with the patient or caregiver.	treatment. (3) Refer the patient for medical evaluation and treatment. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Because Ms. Justus is concerned about the appearance of the wart and because there is significant possibility of transmitting the causative virus to others, pharmacologic treatment of the wart should be considered. Because the wart is a single, small, painless lesion confined to a single area, and the patient has no identifiable exclusions for self-treatment, she can be treated with a nonprescription wart removal product. She can prevent transmitting the wart to others by wearing shoes or covering the wart, especially when working at the local public pool or utilizing the communal showers in the dorm. She should avoid sharing towels or shoes with others.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Salicylic acid in a 40% pad or strip would be a good treatment choice in this situation." See Figure 43-1 and the box "Patient Education for Warts."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Salicylic acid in a 40% strip or pad form is effective for this type of wart, easy to use, and less painful than some other treatment options. Cryotherapy using nonprescription products is another self-care option for the treatment of warts. However, cryotherapy is more painful than salicylic acid, and small warts typically may be adequately treated with salicylic acid."
	"Warts may be effectively treated with nonprescription wart removal products and preventive measures so long as no exclusions to this approach are present and the lesion to be treated is small, with no complicated skin involvement. Self-treatment with salicylic acid is cost-effective and may provide acceptable results in resolving your

Relevant Evaluation Criteria	Scenario/Model Outcome
	wart.”
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	“Be sure to read and follow the directions that come with the wart removal product.” Table 43–3 and the box “Patient Education for Warts” provide information on removing warts safely.
a. Appropriate dose and frequency	Salicylic acid 40% pads/strip products should be applied every 48 hours.
b. Maximum number of days the therapy should be employed.	With salicylic acid therapy, up to 12 weeks may be required for the wart to resolve.
c. Product administration procedures	See Table 43–3 and the box “Patient Education for Warts.”
d. Expected time to onset of relief	See the box “Patient Education for Warts.”
e. Degree of relief that can be reasonably expected	See the box “Patient Education for Warts.”
f. Most common adverse effects	See the box “Patient Education for Warts.”
g. Adverse effects that warrant medical intervention should they occur	See the box “Patient Education for Warts.”

Relevant Evaluation Criteria	Scenario/Model Outcome
h. Patient options in the event that the condition worsens or persists	"If the wart does not resolve after 12 weeks of treatment, see an appropriate health care provider."
i. Product storage requirements	"Store the pads/strips at room temperature and avoid excessive temperatures."
j. Specific non-drug measures	See the box "Patient Education for Warts."
Solicit follow-up questions from patient or caregiver.	"Will the wart spread to other places on my body?"
Answer patient's or caregiver's questions.	"Warts are caused by a virus that is spread from person to person or by touching surfaces that have come in contact with the wart. Warts also may be spread from one area of the body to another by picking at, touching, or rubbing the wart and then touching other susceptible areas of the body. Various nondrug measures are helpful in preventing the spread of warts." See the box "Patient Education for Warts."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Ms. Justus in 4–6 weeks to assess her progress in clearing the wart with the recommended therapy.

Case 43–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the	

Relevant Evaluation Criteria	Scenario/Model Outcome
patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient, an older man who presents with 3 lesions on his left cheek, seeks his pharmacist's self-care recommendations for their removal. The lesions are small and have a rough, cauliflower-textured surface. He has noticed similar lesions during the past 6 months on his hands. He periodically scrapes off the ones on his hands with a knife, but they grow back. No inflammation, bleeding, significant discoloration, or discharge from the lesions on his face is evident.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	None
c. Description of the patient's efforts to relieve the symptoms	The patient has tried using a nonprescription-strength salicylic acid liquid product on the warts on his hands. He states that the lesions "would go away for a while but then come back," so he quit using it and started scraping them off.
d. Patient's identity	George Williams
e. Patient's age, gender, height, and weight	60 years, male, 5 ft 11 in., 180 lb
f. Patient's occupation	Welder
g. Patient's dietary habits	Mr. Williams generally follows a healthy diet.
h. Patient's sleep habits	Averages 6–7 hours of sleep a night.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	<i>Hypertension</i> : lisinopril daily; <i>hypothyroidism</i> : levothyroxine daily
j. Allergies	None
k. History of other adverse	None

Relevant Evaluation Criteria	Scenario/Model Outcome
reactions to medications	
I. Other (describe) -----	None
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Mr. Williams most likely has multiple common warts on his face from autoinoculation with the virus causing the warts on his hands.
3. Identify exclusions for self-treatment (Figure 43-1).	Multiple common warts and warts located on the face
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Recommend self-care with a nonprescription wart removal product and nondrug measures. (2) Recommend self-care until the patient can consult an appropriate health care provider for evaluation and treatment. (3) Refer the patient for medical evaluation and treatment. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Mr. Williams should be referred to an appropriate health care provider for evaluation and treatment.
6. Describe the recommended therapeutic	"You should consult an appropriate health care provider to evaluate and treat the warts."

Relevant Evaluation Criteria	Scenario/Model Outcome
approach to the patient or caregiver.	
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	“Self-treatment is not recommended because the warts are on your face and because you have already used a nonprescription wart removal product without success.”
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	Criterion does not apply in this case.
Solicit follow-up questions from patient or caregiver.	“Is there anything I can do to keep this wart from coming back again after it is treated?”
Answer patient's or caregiver's questions.	“It is common for warts to recur even after treatment, but various self-care measures have been shown to reduce the risk of reinfection.” See the box “Patient Education for Warts.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact Mr. Williams in 1 week to ensure that he has scheduled an appointment with an appropriate health care provider as directed.

Patient Education for Warts

In treating warts, the goals are (1) to eliminate signs and symptoms associated with the warts, (2) to remove the wart without causing scars, (3) to prevent the wart from recurring, and (4) to prevent spreading of warts to other areas of the body or to other persons. To ensure the best possible treatment outcomes, patients must follow product instructions carefully and must consistently use measures to prevent the spread of warts.

Nondrug Measures

- To decrease the chance of getting warts, avoid nail-biting; do not go barefoot; and keep feet clean and dry.
- To avoid spreading warts from one part of your body to another, do not cut, shave, or pick at warts; wash hands before and after treating or touching warts; and use a single specific towel to dry wart-affected areas, taking care to avoid touching skin on other areas of the body with the same towel.
- To avoid spreading warts to others, do not share towels, razors, socks, shoes, and so forth; keep the wart covered; and do not walk barefoot, especially in bathrooms or in public places.

Nonprescription Medications

- Select only nonprescription salicylic acid or cryotherapy products approved for self-treatment for warts. Follow the instructions on the label closely.
- Use these products only on common or plantar warts. Do not use on moles, birthmarks, warts with hairs growing from them, irritated or inflamed skin, or infected skin.
- If you are not certain that the condition is a wart, consult a health care provider before using these products.
- Do not use these products to treat warts on the face, mucous membranes, breasts, or genitals; in the armpits; or around fingernails.
- Do not use these products in women who are pregnant or breastfeeding, or patients who have diabetes or poor circulation, or are immunocompromised.
- Some of these products are flammable or contain collodions that

are poisonous if ingested. Keep away from heat and out of children's reach.

- Warts may recur after treatment.

Salicylic Acid Products

- Do not use salicylic acid products in children who are younger than 3 years of age.
- Keep these products away from the eyes. In the event of contact with the eyes, seek medical help immediately.
- Do not apply these products to healthy skin. In the event of such contact, wash the area with soap and water immediately.
- Improvement should be seen within 1–2 weeks of beginning treatment. The wart should completely clear within 6–12 weeks. Self-treatment should not continue for longer than 12 weeks.

Cryotherapy Products

- Do not use cryotherapy products on children younger than 4 years of age.
- You will feel an aching, stinging sensation when the product is applied.
- A blister will form and the wart should fall off after about 10 days.
- If the wart does not completely clear after the first treatment, the procedure may be repeated in 2 weeks. Cryotherapy products should not be used for more than 12 weeks overall, and the treatment should not be repeated more than 3 times.

When to Seek Medical Attention

- Stop using the products and consult a dermatologist or other appropriate health care provider if severe irritation or pain occurs immediately after application.
- If the wart has not cleared after 12 weeks of treatment, consult a knowledgeable health care provider for evaluation and treatment.

Source: [References 7, 8, 14–16](#), and [18–20](#); U.S. News & World Report and Pharmacy Times. Health: wart removers. Available at:

<http://health.usnews.com/health-products/top-rec-wart-removers-146>. Accessed May 8, 2019; and Compound W [product information]. Lynchburg, VA/Tarrytown, NY: Prestige Brands. Available at: <https://www.compoundw.com/wart-removal-products/salicylic-acid-wart-removal/compoundw-one-step-strip-kids>. Accessed August 8, 2019.

Key Points for Warts

- Because many warts will resolve without treatment, a wait-and-see approach may be an appropriate management option in some patients. However, this approach allows continued transmission of the highly contagious HPV.
- Patients with multiple warts, warts in any area other than the hands and feet, warts on the fingernails, or large warts should be evaluated by an appropriate health care provider.
- Plantar warts should be treated with higher concentrations of salicylic acid (40%). Warts on the hands or areas with thinner epidermis can be treated with lower concentrations of salicylic acid (17%).
- NO and DMEP products are available for home cryotherapy treatments.
- The directions for use of nonprescription salicylic acid and cryotherapy products should be followed carefully to prevent injury to healthy tissue surrounding the wart.
- Patients with diabetes, poor circulation, or immunodeficiency should not self-treat with salicylic acid or cryotherapy without first consulting their regular health care provider.
- Patients who experience adverse effects from nonprescription wart removal products or have warts that recur frequently should be evaluated by an appropriate health care provider.

Chapter 44: Minor Foot Disorders

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The 52 bones of the feet account for one quarter of the bones in the body, reflecting the outsize role of the foot as the literal basis for locomotion. Both the bones and soft tissues of the feet are subject to the attendant stresses of weight-bearing as well as the unique functional maneuvers required for walking as simple forward navigation. The goal for a day's worth of walking to maintain general health is 8000–10,000 steps, adding up to several miles. By the age of 70, the average person may have walked an equivalent of circling the earth nearly four times.

Although it is not “normal” for feet to hurt (under typical usage), up to 75% of Americans will experience foot health problems at some point in their lives.^{1,2} Women are four times more likely to experience foot problems. In the United States, the most common disorders are corns or calluses (5%), ingrown toenails or other nail afflictions (5%), foot infections including athlete's foot and warts (5%), and foot injuries and structural problems—bunions, flat feet, and fallen arches (6%).¹ Many minor foot disorders and injuries occur as a consequence of neglect, lack of awareness of proper foot care, and years, even decades of wear and tear. Accordingly, health care providers likely to encounter patients with foot health problems should maintain clinical awareness of this category of disorders, as well as familiarity with their management, including recognition of specific signs and symptoms, recommendations for effective measures for prevention and treatment, and referrals, when indicated, to a podiatrist or other foot care specialist for further evaluation and management.

The pharmacist may be the first health care provider consulted by a person with a foot-related complaint. At the initial assessment, a thorough history is necessary to ensure that self-care is appropriate for both the patient and the foot problem. In some instances, self-care for foot disorders is inappropriate. For instance, children with congenital malformations, deformities, or specific diseases that affect the foot (e.g., juvenile arthritis) require medical management by an orthopedic surgeon or a podiatrist. Rapid growth in adolescents can result in foot irritation from changes in growth plates, which is a condition excluded from use of self-care measures. Older patients may present with foot problems related to aging (e.g., arthritis) or disease (e.g., peripheral vascular disease). Common foot disorders may potentially have

severe consequences in patients with comorbid diseases (e.g., diabetes) and also may indicate other serious underlying conditions.³ In some instances, inappropriate foot care practices may be life-threatening in patients with diabetes, severe arthritis, or impaired circulation^{3–6} (see the box “A Word About Chronic Diseases and Foot Disorders”). For some patients, however, foot problems causing mild to moderate discomfort and impaired mobility can be treated with self-care measures. Examples of such conditions are corns, calluses, ingrown toenails, tired/aching feet, and exercise-induced injuries.

Pathophysiology of the Foot

At birth, the infant’s foot has 33 joints, 19 muscles, 107 ligaments, and cartilage that will develop into 26 bones. The feet continue to develop and mature until the ages of 14–16 years for females and 15–21 years for males. There may be increased foot pain and soft tissue stiffness with a decreased range of motion and strength with advancing age. Such changes lead, in turn, to altered gait, with an increased risk of falls.⁷ After years of bearing the body’s weight, feet tend to broaden and flatten, thereby stretching ligaments and causing bones to shift position. This altered anatomy subjects the feet to stress even in the absence of overuse, which is then compounded by prolonged standing. Additionally, feet often are the first area of the body to exhibit clinical manifestations of conditions such as arthritis, diabetes, and neurologic or circulatory disorders.¹

Corns and Calluses

Corns and calluses are common foot disorders that often are overlooked by the affected patients themselves. However, these lesions may indicate a biomechanical problem, with potentially serious complications if the underlying condition is left untreated. When the clinical presentation includes a foot-related concern, even if the patient minimizes the issue, the initial assessment often will reveal the presence of such lesions. The health care provider should then attempt to identify any contributing factors in their pathogenesis, as well as recommend appropriate treatment.

Pathophysiology of Corns and Calluses

Under normal conditions, the cells in the skin's basal cell layer (*stratum basale*) undergo mitotic division at a rate that balances the continual surface cellular desquamation, eventuating in complete replacement of the epidermis in approximately 1 month. During corn or callus development, however, friction and pressure increase mitotic activity of the basal cell layer, leading to the migration of maturing cells through the prickly cell (*stratum spinosum*) and granular (*stratum granulosum*) skin layers (see [Chapter 33](#), Figure 33–1). As more cells reach the outer skin surface, they produce a thicker, horny layer (*stratum corneum*). This process is a natural protective mechanism of the skin surface and may signal biomechanical problems that result in abnormal weight distribution on the foot. When friction or pressure is relieved, mitotic activity returns to normal, with consequent remission and disappearance of the lesion.^{8,9}

A Word about Chronic Diseases and Foot Disorders

Some chronic diseases can predispose affected patients to foot complications. Patients with diabetes often have poor circulation and diminished limb sensitivity, making them especially vulnerable to infectious foot problems. Other susceptible patients include those with peripheral vascular disease or arthritis. Whether or not the clinical presentation includes foot-related complaints, questioning about daily medication use or a review of the patient's drug profile can alert the health care provider to the presence of such chronic diseases. Typical drug use patterns for high-risk patients include regimens of insulin, oral or injectable antidiabetic drugs, drugs for circulation disorders (e.g., clopidogrel, pentoxifylline); drugs for neuropathic pain (e.g., gabapentin, pregabalin, duloxetine); and drugs for arthritic disorders (e.g., acetaminophen, NSAIDs).

If not properly supervised in patients with impaired circulation, self-treatment with nonprescription products may induce more inflammation, ulceration, or even gangrene, particularly in cases of vascular insufficiency in the foot. Affected tissues in patients with diabetes and those with

peripheral circulatory impairments are particularly susceptible to development of gangrene. In addition, simple lesions may mask more serious abscesses or ulcerations. Without proper care, these underlying problems may lead to conditions such as osteomyelitis, which may necessitate hospitalization and aggressive intravenous antibiotic therapy.

Diabetes Mellitus

Poorly controlled diabetes is associated with increased health care costs, decreased quality of life, and increased morbidity and mortality. Additionally, affected patients are at a greater risk for lower extremity complications. Peripheral neuropathy, which results in loss of injury perception, and excessive plantar pressure are the two major causes of foot ulcerations. Plantar pressure contributes to decreased mobility and development of foot deformities. Poor foot hygiene, such as extremely hot water soaks, wearing inappropriate footwear, and lack of daily foot self-examinations, contributes to foot complications in patients with diabetes. Patients with this disorder need to be educated on proper foot care, such as trimming toenails appropriately, not applying creams/lotions between the toes, keeping socks clean and dry, and performing foot examinations at home. The following self-care and preventive measures can help reduce the risk of diabetic complications.

Foot Care

- All patients should have a yearly comprehensive foot evaluation. Evaluation should include assessing for any changes in foot appearance or tactile sensation.
- The 2019 American Diabetes Association (ADA) Standards of Care state that only patients with evidence of sensory loss or history of ulceration/amputation should have their feet inspected at every primary care provider visit.
- Advise patients at high risk for development of skin ulcers (e.g., those with neuropathy) to see a podiatrist regularly.
- Teach patient to clean and inspect feet daily for any changes (e.g., corn, callus, open wound, evidence of fungal infection).
- Instruct patient to trim nails carefully (straight across) and file them

with an emery board to the contour of the toe.

- Instruct patient to avoid walking barefoot.
- Recommend use of soft cotton, synthetic blend, or wool socks to absorb moisture.
- Recommend that patient wear proper-fitting, comfortable shoes and use caution when “breaking in” new shoes. Consider the use of specialized therapeutic footwear, especially in patients with severe neuropathy, foot deformity, or previous amputation.
- Recommend that patient inspect shoes for foreign objects before inserting feet.
- Recommend that patient (1) use moisturizing lotion sparingly on the tops and bottoms of dry feet, (2) allow feet to completely dry before donning shoes, to prevent excess moisture buildup, and (3) avoid use of moisturizers between the toes.

Peripheral Vascular Disease

Patients with peripheral vascular disease often have poor circulation in the feet and legs. Because of decreased blood flow and low oxygen perfusion, skin ulcerations and decreased wound healing may be problematic in these patients. They may complain of persistent and unusual feelings of cold, numbness, tingling, burning, or fatigue. Other manifestations of this disease may include discolored skin, dry skin, absence of hair on the feet or legs, or a cramping or tightness in the leg muscles. The health care provider should palpate for pedal pulses. The clinical interview also should include the following two important questions: (1) “Do you experience aching in your calves when you walk?” (2) “Do you have to hang your feet over the edge of the bed during sleep to relieve the soreness in your calves?” A yes response to either question warrants referral to a medical provider.

Localized redness or unilateral coldness may indicate a possible blockage (a clot) of circulation to the foot. The involved foot or lower leg may be physically larger than the other, may have a reddened or waxy appearance to the skin, may feature absence of hair growth on the toes, and will exhibit thickened nails. With suspected circulatory problems, if the patient’s medication history does not list preparations and products

intended to relieve such symptoms, immediate referral for further evaluation is warranted.

A daily footbath is a simple measure for managing peripheral vascular disease. After the foot is patted dry, an emollient foot cream can be applied to aid the skin in retaining moisture and pliability. The footbath also will soften brittle toenails for clipping and filing. The feet should be kept warm and moderately exercised every day.

Arthritis

Osteoarthritis is a noninflammatory, degenerative joint disease that occurs primarily in older people. Degeneration of the articular cartilage and changes in the bone result in a loss of resilience and a decrease in the skeleton's shock absorption capability. This condition, however, also is experienced by young persons in their late teens and early 20s as a secondary complication of a previous athletic injury. In this scenario, osteoarthritis can be evidenced by the development of *hallux limitus* (i.e., pain on flexion or extension of the big toe related to stiffness and spur formation in the metatarsophalangeal joint) or *rigidus* of the big toe (a stiff toe, unable to move). Subsequently, affected patients experience considerable difficulty with their shoes not fitting properly. Development of an osteoarthritic condition in the ankle joint is another possible complication. Referral for further evaluation is appropriate.

Most patients with rheumatoid arthritis eventually have foot involvement. The major forefoot deformities in these patients are painful metatarsal heads, hallux valgus, and clawfoot. Corrective surgical procedures often are indicated to reduce pain and improve function and mobility. Evidence for the efficacy of conventional nonsurgical therapy (e.g., orthopedic shoes, metatarsal inserts, conventional arch supports, metatarsal bars) is limited.

Proper palliative foot care is especially important for patients with arthritis that affects the feet. They should wear properly fitted shoes, pad their shoes with insoles to protect the feet from the shock of hard surfaces, and undergo regular podiatric or medical examinations.

Key: NSAID = Nonsteroidal anti-inflammatory drug.

Source: American Diabetes Association. Standards of medical care in diabetes—2019. *Diabetes Care*. 2019;42 (Suppl 1):S1–S2. doi: 10.2337/dc19-Sint01; *National Diabetes Facts Sheet: National Estimates and General Information on Diabetes and Prediabetes in the United States, 2011*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2011; Evert AB, Boucher JL, Cypress M, et al. Nutrition therapy recommendations for the management of adults with diabetes. *Diabetes Care*. 2013;36(11):3821–42; and Mullooly CA. Physical activity. In: Mensing C, ed. *The Art and Science of Diabetes Self-Management Education*. 1st ed. Chicago, IL: American Association of Diabetes Educators; 2006:297–330.

Clinical Presentation of Corns and Calluses

Corns and calluses are similar in that both produce a marked hyperkeratosis of the stratum corneum, but they have marked clinical differences.

Corns

A *corn (clavus)* is a small, raised, sharply demarcated, hyperkeratotic lesion with a central core; the lesion is caused by pressure from underlying bony prominences or joints. The central core of the corn differentiates it from a wart (see [Chapter 43](#), [Table 43–5](#)). Misidentification of warts as corns is common. A corn has a hard center, whereas a wart will bleed because of the multiple capillary loops in its center.⁸ Corns generally are well circumscribed, with a diameter of 1 cm or less, and presentation may range from flesh-colored to white to yellowish gray. The base of the corn is on the skin surface; its apex points inward and presses on the nerve endings in the dermis, causing pain.^{8–11}

Polished, shiny, dry *hard corns (heloma durum)* are the most prevalent and usually occur on the bulb of the great toe, the dorsum of the fourth or fifth toe, or tips of the middle toes. *Soft corns (heloma molle)* are whitish thickenings of the skin and may be extremely painful. Accumulated perspiration macerates the epidermis, giving this corn a soft appearance. Soft corns may occur between any adjacent toes but most frequently are found between the fourth

and fifth toes⁹ (Figure 44–1).

FIGURE 44–1 Disorders affecting top and sole of foot: corns, callus, and plantar warts.

Pressure from inappropriate, tight-fitting shoes is the most frequent cause of pain from corns. As narrow-toed or high-heeled shoes crowd toes into a narrow toe box, the most lateral toe, the fifth, sustains the most pressure and friction and is the usual site of a corn. The resulting pain may be severe and sharp (on application of downward pressure) or dull and discomforting. Consumer research suggests that approximately 82% of women 35–54 years of age suffer moderate to severe pain from corns, with 35% consequently limited or restricted in their activities.^{7,10,11}

Calluses

A *callus* has a broad base, with relatively even thickening of skin, and generally is found on the bottom of the foot in areas such as the heel, ball of the foot, and toes, and on the sides of the foot (Figure 44–1). A callus has indefinite borders and ranges in diameter from a few millimeters to several centimeters. The lack of defined borders helps in differentiating calluses from corns, which have well-circumscribed margins. A callus usually is raised and yellow, with a normal pattern of skin ridges on its surface. Calluses form over joints and on weight-bearing areas of the hands and feet^{7,9–12} (see Color Plates, photograph 35).

Friction (caused by loose-fitting shoes or tight-fitting hosiery), walking barefoot, and structural biomechanical problems contribute to the development of calluses. Calluses can be both symptomatic and protective.

Two of the most common calluses found on the feet are discrete-nucleated and diffuse-shearing calluses. The *discrete-nucleated callus* is smaller and has a localized translucent center; this type of callus is painful with applied pressure because of its central keratin plug. The *diffuse-shearing callus* covers a larger surface area and does not have a central core, so it is not associated with pain.¹³

Treatment of Corns and Calluses

Treatment Goals

The goals of self-treatment are (1) to provide symptomatic relief, (2) to remove corns and calluses, and (3) to prevent their recurrence by correcting underlying causes.

General Treatment Approach

Although effective nonprescription products are available for removing corns and calluses, ultimate success depends on eliminating the causes. The algorithm in [Figure 44–2](#) outlines self-treatment for corns and calluses and lists potential exclusions for self-care.

Nonpharmacologic Therapy

Daily soaking of the affected skin area (for at least 5 minutes in warm, not hot, water) throughout the treatment period aids in softening dead tissue for removal. After normal washing of the foot, dead tissue should be removed gently, rather than forcibly, to avoid further damage. A callus file or pumice stone effectively accomplishes this purpose. Power-operated foot files may be too aggressive. Sharp knives or razor blades should not be used because these instruments may lacerate the skin, which could allow bacteria to enter the wound, potentially resulting in localized infection.⁸

Circular foam cushioning pads may aid in relieving painful pressure from inflamed tissue. Polymer gel pads provide a protective cushion without leaving a sticky residue. The gel pads also have a smooth outer surface that does not snag on socks and other hosiery.⁸ A silicone toe sleeve impregnated with mineral oil, such as the Pedifix Visco-Gel Toe Protector, is an option for toes affected by corns. The mineral oil is slowly released to soften the skin. The sleeve protects and cushions the corn area. A foam spacer or lamb's wool may be used to provide relief in areas with soft corns. Placement of a metatarsal pad or lamb's wool may help relieve pain and pressure from a callus.¹³

Eliminating the pressure and friction that induce corns and calluses entails using well-fitting, nonbinding footwear that evenly distributes body weight¹³ ([Table 44–1](#)). The stratum corneum will normalize after topical keratolytics are applied and total desquamation of the hyperkeratotic tissue occurs. For anatomic foot deformities, orthopedic corrections must be made. Orthotics

(i.e., arch supports) may be needed to help compensate for deformities by redistributing the mechanical forces incurred by the foot. These measures relieve pressure and friction, which allows normal mitosis of the basal cell layer to resume. Ultimately, surgical correction of toe deformities with resection of the underlying bone may be necessary.

TABLE 44-1 Selection of Proper-Fitting Footwear

- Buy shoes in the proper size (width and length). To obtain an accurate measurement, ask a trained salesperson to measure your feet. Recheck shoe size every 2 years.
- Base shoe length on the longest toe of your longest foot. The optimum distance between the tip of the shoe and the longest toe is approximately $\frac{1}{2}$ inch. In an athletic shoe, 1 inch is needed.
- For proper arch length, choose a shoe in which the first metatarsal head of the foot fits the metatarsal “break” of the shoe.
- For proper shoe width, choose a shoe that feels comfortable at the first metatarsal joint (so that toes do not feel cramped in the toe box).
- Once the shoe size is determined, choose a shoe shaped to match the shape of your foot.
- If you have abnormalities of the toes (e.g., hammer toes) or use orthotics or padding in your shoes, select a shoe with a toe box of adequate depth (vertical height) to prevent friction on the tops of the toes. A wide toe box will help relieve pressure between toes.
- Make sure the heel area fits snugly and helps hold the foot straight.
- If you are physically active, make sure the shoe’s midsole provides adequate cushioning and support.
- Try on both shoes at the time of purchase, preferably wearing a pair of socks or stockings of the type that will usually be worn with the new shoes.
- If your feet tend to swell, shop for shoes at the end of the day.

Source: [References 1, 16, and 25](#); and How your feet work—and three steps for keeping them healthy. *Harvard Health Lett.* 2009;34(10):3–5. PMID: 20821859.

Pharmacologic Therapy

Salicylic Acid

Salicylic acid, a keratolytic agent, is formulated in various strengths (0.5%–40%). For the treatment of corns and calluses, the approved concentration ranges are 6%–17% in a topical gel, 12%–40% in a plaster vehicle, and 12%–27.5% in a collodion-like vehicle.^{14,15}

Salicylic acid is believed to act on hyperplastic keratin, without affecting viable

epidermis. On application of salicylic acid, the treated area will swell, soften, macerate, and then desquamate the affected epithelium. The U.S. Food and Drug Administration (FDA) has stated that presoaking the affected area before application of salicylic acid produced no significant positive effects. In its final rule, FDA proposed allowing manufacturers of these products to use the following statement as an optional direction to the consumer: “May soak corn/callus (or wart) in warm water for 5 minutes” to assist in removal.^{14,15}

The FDA advisory review panel evaluated more than 20 agents for the treatment of corns and calluses. Of these agents, only salicylic acid in a plaster, pad, disk, gel, or collodion-like vehicle dosage form is approved as safe and effective as a nonprescription preparation marketed for the removal of corns and calluses (Table 44–2). FDA recognizes that the term *plaster* includes disks and pads, because these dosage forms are similar.¹⁵

TABLE 44–2 Selected Corn and Callus Removal Products	
Trade Name	Primary Ingredient
Pedinol Hydrisalic Gel	Salicylic acid 17%
Dr. Scholl’s Corn/Callus Remover Liquid	Salicylic acid 17%
Dr. Scholl’s Duragel Callus Remover	Salicylic acid 40%
Dr. Scholl’s Duragel Corn Remover	Salicylic acid 40%
Curad Mediplast Corn, Callus & Wart Remover Pad	Salicylic acid 40%

Source: Reference 14.

Salicylic acid usually is applied to a corn, callus, or common wart in a collodion-like vehicle. These vehicles contain pyroxylin and various combinations of volatile solvents (e.g., ether, acetone, alcohol) or a plasticizer, which usually is castor oil. Pyroxylin is a nitrocellulose derivative that remains on the skin as a water-repellent film after the volatile solvents have evaporated.^{14,15}

The advantages of collodions and liquid dosage forms are that they form an adherent flexible or rigid film and prevent moisture evaporation. These

properties aid penetration of the active ingredient into the affected tissue, resulting in sustained local action of the drug. The delivery systems are largely water-insoluble, as are most of their active ingredients, including salicylic acid. They also are less prone than other liquid solutions to run onto surrounding skin.^{14,15}

A disadvantage of collodions is that they are extremely flammable and volatile. Some patients may inhale and abuse these vehicles. Another disadvantage is their occlusion of normal water transport through the skin, which allows systemic absorption of some drugs (e.g., salicylic acid). Percutaneous absorption may be problematic with prolonged use on large surface areas in children and patients with renal or hepatic impairment, because salicylic acid is largely metabolized in the liver and excreted in the urine. Although occlusive vehicles can enhance the percutaneous absorption of salicylic acid, it is highly unlikely that salicylate toxicity will result during corn, callus, or wart therapy at recommended dosages. However, if signs and symptoms of possible salicylic toxicity (nausea, vomiting, dizziness, hearing loss, tinnitus, lethargy, hyperpnea, diarrhea, or psychiatric disturbances) emerge, use of these products should be discontinued immediately.^{14,15}

Salicylic acid also may be delivered to the skin through the use of a plaster, disk, or pad. Such delivery systems provide direct and prolonged contact of the drug with the affected area, resulting in quicker resolution of the condition. Salicylic acid plaster is a uniform solid or semisolid adhesive mixture of salicylic acid in a suitable base that is spread on appropriate backing material (e.g., felt, moleskin, cotton, plastic). The usual concentration of salicylic acid in the base is 40%; with these dosage forms, the preparation may be applied directly to the corn or callus.^{8,14,15} **Table 44–3** provides instructions for applying salicylic acid products.

TABLE 44–3 Guidelines for Treating Corns and Calluses With Salicylic Acid Products

- Wash and dry the affected area thoroughly before applying any product.
- Soak the affected foot in warm water for 5 minutes. Then remove the macerated, soft white skin of the corn or callus by scrubbing gently with a rough towel, pumice stone, or callus file. Do not debride the healthy skin.

Salicylic Acid 17% in Collodion-Like Vehicle

- Apply product no more than twice daily for up to 14 days. Morning and evening usually are the most convenient times.
- Do not let adjacent areas of normal healthy skin come in contact with product. If this happens, immediately wash off the solution with soap and water.
 - A coating of petroleum jelly on healthy surrounding skin will serve as protection if delivery of the medication accidentally extends beyond the intended treatment area.
- Apply 1 drop at a time directly to the corn or callus until the affected area is well covered. Do not overuse the product.
- Allow the drops to dry and harden so that the solution does not run.
- After use, cap the container tightly to prevent evaporation, which would result in a higher, potentially harmful concentration of the active ingredients.
- Store the product in an amber or otherwise light-resistant container away from direct sunlight or heat.

Salicylic Acid 40% Plasters/Pads

- If using a plaster, trim it to follow the contours of the corn or callus. Apply the plaster to the affected skin, and cover it with adhesive occlusive tape.
- If using medicated disks with pads, apply the appropriate-sized disk directly on the affected area, and then cover the disk with the pad.
- Remove the plaster/pad and occlusive tape within 48 hours.
- After rubbing off the softened skin, reapply the plaster every 48 hours as needed to remove the corn/callus, but do not treat for longer than 14 days—that is, use no more than 7 applications.
 - Seek medical attention if redness or irritation of the skin occurs or if corn or callus is not removed after 14 days of treatment.

Source: [Reference 14](#).

Caution is essential in applying topical salicylic acid because of the risk of inflammation or ulcer formation with suboptimal technique (see the box “A Word About Chronic Diseases and Foot Disorders”). Use of these products may be hazardous in pregnancy, and they should not be used in patients who are breastfeeding because of adverse effects from systemic absorption and the potential for Reye syndrome. Salicylic acid may be used in pediatric patients older than 2 years at concentrations of 1.8%–6%. FDA requires the following warning on salicylic acid product labels:

Do not use this product on irritated skin, any area that is infected or reddened, moles, birthmarks, warts with hair growing from them, genital warts, warts on the face, or warts on the mucous membranes, such as inside the mouth, nose, anus, genitals, or lips. Do not use if you are diabetic, or if you have poor blood circulation.^{14,15}

Assessment of Corns and Calluses: A Case-Based Approach

The assessment should be in a private area where the patient can be comfortable removing the shoe(s) to allow direct inspection of the feet. The patient should be asked about any self-care attempts and their outcome. The patient's health status and current medication regimen also should be assessed. Additionally, lifestyle factors (e.g., occupation, daily exercise, footwear), underlying pathology (e.g., circulatory or neurologic disorders), the possibility of an aggravating event, and the walking/working surface must be evaluated. This information should be recorded and regularly updated in the patient's medical chart. [Figure 44–2](#) illustrates the assessment of a patient with corns or calluses.

Patient Counseling for Corns and Calluses

Remission of corns and calluses can take several days to several months. Patients with such lesions should recognize that effective treatment and maintenance depend on eliminating predisposing factors that contributed to the foot problem. It is important to emphasize the need for wearing footwear of adequate width and length. Pads and cushions also help to reduce the pressure and shearing associated with corn and callus development.

The patient or caregiver should be counseled on how to use nonprescription medications that remove corns and calluses. Because many such products contain corrosive materials, they must be applied only to the corn or callus. Patients should be alerted that products containing collodions are poisonous when ingested and that these products, as well as all other medications, should be stored out of children's reach. Case 44–1 illustrates the assessment of a patient with calluses. The box "Patient Education for Corns and Calluses" lists specific information to provide in patient counseling.

Evaluation of Patient Outcomes for Corns and Calluses

The progress of the patient’s self-treatment regimen for corns or calluses should be checked after 14 days. The affected area should be visually inspected to determine whether the corns or calluses have decreased in size or resolved. The methods used to eliminate the corns or calluses also should be evaluated. If these conditions are still present, the patient should seek further medical evaluation.

Algorithm: Corns and Calluses

FIGURE 44–2 Self-care for corns and calluses.

Case 44–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient’s symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient describes a large flesh-colored, thick dry area of “dead skin” on the ball of her foot that has been present for approximately 6 weeks. She has recently started wearing a new pair of shoes with heels to work.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient’s symptom(s)	The patient states that the thickened area bothers her when she walks and runs.
c. Description of the	She has tried wearing thicker socks and using a pumice stone

Relevant Evaluation Criteria	Scenario/Model Outcome
patient's efforts to relieve the symptoms	to remove excess skin on the affected area, but the excess tissue comes back.
d. Patient's identity	Janice Jones
e. Patient's age, gender, height, and weight	35 years, female, 5 ft 2 in., 126 lb
f. Patient's occupation	Banker
g. Patient's dietary habits	Smoothie for breakfast, salad or sandwich for lunch; dinner typically consists of a protein and carbohydrate (e.g., chicken and rice, falafel sandwich, spaghetti with meatballs).
h. Patient's sleep habits	She sleeps 7 hours nightly.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	No pertinent medical conditions
j. Allergies	Penicillin–rash
k. History of other adverse reactions to medications	None
l. Other (describe) _____	None
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Ms. Jones has developed diffuse shearing calluses (Figure 44-1).
3. Identify exclusions for self-treatment.	None (Figure 44-2)
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to	Options include (1) Refer Ms. Jones to an appropriate health care provider.

Relevant Evaluation Criteria	Scenario/Model Outcome
determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	(2) Recommend self-care with a nonprescription callus remover and nondrug measures. (3) Recommend self-care until Ms. Jones can see an appropriate health care provider. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Ms. Jones should use a nonprescription callus remover, callus cushioning pads, and nondrug measures to treat this condition.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Daily foot soaks and a pumice stone or foot file may be used to reduce roughness of your calluses. Completely dry the feet before applying the callus remover. Use of cushioning pads will help protect pressure point areas on your feet, allowing the affected skin to improve. The shoes you recently started wearing may be causing the calluses—you also should consider getting fitted for appropriate shoes." See Table 44-1 .
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Calluses can be removed by nonprescription products and the use of foot files. However, it is important to assess the cause of the callus formation and to correct the cause with appropriate measures including selection of proper-fitting footwear."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	See Table 44-3 for instructions for applying salicylic acid products. Also see the box "Patient Education for Corns and Calluses." Ms. Jones should experience a response to treatment recommendations within 14 days.
Solicit follow-up questions	(1) "How long do I really need to use this product?"

Relevant Evaluation Criteria	Scenario/Model Outcome
from the patient or caregiver.	(2) Can I speed up the process by cutting down the callus with a razor blade before applying the nonprescription medication?" (3) "I really like wearing my new shoes—do I have to stop?"
Answer the patient's or caregiver's questions.	(1) "You should follow the appropriate treatment duration to receive the maximum benefit. You should experience resolution of symptoms within 14 days." (2) "It is best to soak the feet and use foot files to pare down the callus. Do not cut on your feet because of the risk of injury with subsequent infection." (3) "Unfortunately, your new shoes may be the underlying cause for this condition. It does seem like shoes that are good for the feet may not look as fashion-forward as wanted. Talk to a foot care specialist to see if certain types of shoes or padding would be your best options to maintain foot health."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Ask Ms. Jones to call in 14 days to update you on the response to your treatment recommendations, or you could call her into the pharmacy to evaluate the response.

Patient Education for Corns and Calluses

The objectives of self-treatment are (1) to provide symptomatic relief, (2) to remove corns or calluses, and (3) to prevent their recurrence by correcting underlying causes. For most patients, carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

Nondrug Measures

- After use, carefully clean instruments used to remove dead skin, to

avoid bacterial contamination with potential infection on subsequent use.

- Do not use sharp knives or razor blades to remove dead skin from corns and calluses. Accidental cuts into the dermis with such instruments may lead to bacterial infections.
- If you have trouble applying the product only to the affected area, use petroleum jelly to coat healthy skin surrounding the treatment area before applying the corn and callus remover.
- For temporary relief of painful pressure in the area under a corn or callus, cover the affected area with a pad.
- Consult an appropriate health care provider if the symptoms described recur.

Preventive Measures

- To eliminate the pressure and friction that cause corns and calluses, wear well-fitted shoes that evenly distribute body weight (Table 44-1).
- Consult a podiatrist about foot deformity corrections.

Nonprescription Medications

- To remove corns and calluses, use a salicylic acid product labeled for use on these types of lesions (Tables 44-2 and 44-3).
- Do not use this product on irritated, infected, or reddened skin.
- Do not use this product if you are diabetic or have poor blood circulation.
- Salicylic acid is poisonous. Do not allow it to come in contact with the mouth, and keep it out of children's reach.
- Note that the medication sloughs off skin, which may leave an unsightly pinkish tinge to the affected area.

When to Seek Medical Attention

- Stop treatment and consult an appropriate health care provider if swelling, reddening, or irritation of the skin develops, or if pain occurs immediately with product application.

Tired, Aching Feet and Exercise-Induced Foot Injuries

With every step taken, gravity-induced pressure of up to twice the body's weight bears down on each foot, releasing powerful shocks of energy that the foot's natural padding must struggle to absorb.¹ In an unpadded shoe, the shock as the foot strikes the ground is transmitted through the foot to the ankle, leg, and back. This shock can fatigue muscles, resulting in tired, aching feet and/or back pain.^{16,17}

An estimated two thirds of Americans complain of tired, aching feet (the most common foot problem). In addition, 2 million adults are estimated to suffer from heel pain.¹⁸ In addition to recognizing the foot disorders due to daily impact, health care providers should be familiar with possible exercise-induced foot injuries, particularly those caused by running, jogging, or other high-impact physical activities (Figure 44–3). People seeking to increase their daily activity level may oftentimes plunge head first into a strenuous exercise program without understanding important precautions to avoid injury. To minimize the risk of injury, persons who are typically sedentary, are older than 35 years of age, suffer from hypertension, or have a history of heart disease or diabetes should seek medical evaluation before beginning a high-level exercise regimen.¹⁹ Patients with potential orthopedic problems may benefit from walking instead of engaging in more demanding activities.²⁰

FIGURE 44–3 Anatomic locations for selected foot and leg injuries associated with excessive impact shock.

Pathophysiology of Tired, Aching Feet and Exercise-Induced Foot Injuries

Aching feet can be caused by increased frequency of standing and/or walking (especially on hard surfaces), age-related erosion of the fat padding on the bottom of the foot, circulatory or neurologic disorders, and poor-fitting or inappropriate footwear.

Because the cause of heel pain is difficult to determine, treatment often can

be prolonged and expensive. The three most common types of heel pain are heel spurs, plantar fasciitis, and Sever's disease. Exercise-induced injuries include shin splints, stress fractures, Achilles tendonitis, blisters, ankle sprains, intermetatarsal neuritis, and toenail loss. The common causes, pathophysiologic mechanisms, clinical presentation, and therapeutic recommendations are summarized in [Table 44–4](#) for each of these conditions.

TABLE 44–4 Differentiation and Management of Exercise-Induced Foot Injuries

Type of Injury	Common Cause(s)	Pathophysiologic Mechanism(s)	Clinical Presentation	Recommendation(s)
Shin splints	Overzealous workout; inappropriate stretching; running/walking on sloped or hard surfaces; wearing ill-fitting footwear; overstriding	Excessive pronation weakening/straining posterior tibialis; anterior tibia muscle stretching away from periosteum that lines shin bone	Pain in medial lower third of shin, or below knee and above ankle; worsening pain with exercise; cramping, burning, and tightness on anterior lateral section of shin	PRICE or RICE therapy; acetaminophen or ibuprofen; shoe orthotic; medical referral
Stress fracture	Running on hard, rigid surfaces; rapid increase in physical activity; jumping; estrogen deficiency; nutritional deficiencies; obesity; ill-fitting footwear	Outer cortex of long bones of leg or foot cracking from tensile forces transmitted by ligaments, tendons, and muscles	Deep pain in lower leg; tenderness to touch; swelling; worsening pain with exercise	Medical referral; complete rest; NSAID therapy
Achilles tendonitis	Running on hills or in sand; ill-fitting footwear;	Inflammation of Achilles tendon; rupture of tendon	Posterior heel pain; tenderness; swelling	Medical referral

Type of Injury	Common Cause(s)	Pathophysiologic Mechanism(s)	Clinical Presentation	Recommendation(s)
	excessive pronation; arthritis			
Blisters	Repetitive movement; ill-fitting footwear; tight hosiery	Continual friction on small surface of foot separates stratum corneum and stratum lucidum skin layers, causing space between layers to fill with fluid	Accumulation of fluid beneath stratum corneum; may be painful	Do not remove blister; protect with topical bandage; medical referral for drainage may be indicated.
Ankle sprains	Ankle rotation outside acceptable range	Lateral ligament damage	Pain; bruising; tenderness; difficulty walking	PRICE or RICE therapy; compression bandage
Intermetatarsal neuritis	Small toe box space	Inflammation of nerves from compression of or entanglement between metatarsal heads and digital bases	Pain and numbness between toes	Proper footwear
Toenail loss	Long, thick toenails in small toe box space; friction and pressure from running in “stop and go” sports such as tennis	Fluid beneath nail plate elevating toenail from nail bed	Dark discoloration from blood underneath nail plate; pain at toe; nail loss	Referral to podiatrist or qualified primary care provider
Plantar fasciitis	High arches, flat feet, repetitive stress during athletic activity, pronated feet,	Strain on the connective tissue that attaches the arch to the front of the heel	Manifests with pain on arising in the morning or on standing up after sitting; the pain	

Type of Injury	Common Cause(s)	Pathophysiologic Mechanism(s)	Clinical Presentation	Recommendation(s)
	prolonged standing		results from tissue contraction. The sensation on the bottom of the heel is quite painful, and the patient may complain of a burning sensation.	
Heel spurs	Incorrect walking or running technique, excessive running, poor-fitting shoes, obesity, aging	Bony growth on the underside of the heel bone Possible formation of calcium deposits on the calcaneous bone (detected via x-ray imaging), causing pain of increasing intensity after prolonged periods of rest	Strained foot muscles, deterioration of fat tissue surrounding heel bone	
Sever's disease	Seen in children (predominantly occurs in boys 8-15 years of age), manifested as heel pain precipitated by running, jumping, or excessive walking; usually resolves on completion of bone growth	Calcaneal apophysitis	Manifests with no swelling, skin changes, erythema, or other visible abnormalities. The <i>squeeze test</i> aids in the diagnosis of Sever's disease: Pressure is applied at point of attachment of the	

Type of Injury	Common Cause(s)	Pathophysiologic Mechanism(s)	Clinical Presentation	Recommendation(s)
	or with curtailment of activity		calcaneal apophysis to main body of the os calcis to determine if the patient experiences pain.	

Key: NSAID = Nonsteroidal anti-inflammatory drug; PRICE = protection, rest, ice, compression, elevation; RICE = rest, ice, compression, elevation.

Source: [References 8, 11, 17, 19](#), and [21–32](#).

Assessment of Tired, Aching Feet and Exercise-Induced Foot Injuries

Treatment of tired, aching feet requires evaluation of lifestyle factors (e.g., occupation, daily exercise, footwear); the possibility of underlying disease (e.g., circulatory or neurologic disorders) or an aggravating event; and the walking/working surface. If an underlying pathologic condition is suspected, the patient should be referred to a primary care provider or podiatrist for further evaluation. Case 44–2 illustrates the assessment of a patient with tired, aching feet.

Case 44–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	

Relevant Evaluation Criteria	Scenario/Model Outcome
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient presents complaining of "tired, achy feet" that started approximately 2 weeks ago. Her right foot hurts more than the left, but both are affected.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Walking makes the symptoms worse, and the patient is upset about this because she likes to be active. She recently went for a strenuous hike, and since then, her feet have been hurting more than usual. Resting brings some relief.
c. Description of the patient's efforts to relieve the symptoms	The patient visited a local health spa for a foot massage, but that helped only temporarily.
d. Patient's identity	Agnes Martin
e. Patient's age, gender, height, and weight	61 years, female, 5 ft 7 in., 150 lb
f. Patient's occupation	Retired sports equipment sales associate
g. Patient's dietary habits	Eats a relatively healthy diet, 2-3 meals a day.
h. Patient's sleep habits	Typically sleeps 8 hours per night.
i. Concurrent medical conditions,	Diabetes type 1: takes insulin glargine 40 units daily and insulin aspart 10 units AC meals

Relevant Evaluation Criteria	Scenario/Model Outcome
prescription and nonprescription medications, and dietary supplements	
j. Allergies	NKDA
k. History of other adverse reactions to medications	None
l. Other (describe) -----	
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	The patient has tired, aching feet, which may be due to strenuous activity, possibly inappropriate footwear, and changes in anatomy due to aging.
3. Identify exclusions for self-treatment (Figure 44-5).	Diabetes
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer Mrs. Martin to an appropriate health care provider for further evaluation. (2) Recommend self-care with nonprescription products for treating tired, aching feet. (3) Recommend self-care until Mrs. Martin can see an appropriate provider. (4) Take no action.

Relevant Evaluation Criteria	Scenario/Model Outcome
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Mrs. Martin should consult a podiatrist because she has diabetes. She may benefit from a podiatrist's evaluation to ensure that she has appropriate footwear, especially for her strenuous activities. She also should rest her feet until the pain is alleviated. She can take a nonprescription pain medication such as acetaminophen to help relieve discomfort until her specialist appointment.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"You should consult an appropriate health care provider about your tired, aching feet. Especially because you have diabetes, it's important that someone monitor the condition of your feet and check that you are wearing the most appropriate footwear. You may take acetaminophen for at least partial relief of the pain, and continuing to rest until you restart your strenuous activities may help too."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"This option is best for you since you typically are so active and you have a health condition that may put you at risk for worsening foot problems."
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	"Definitely rest your feet as much as possible. If the pain continues, take acetaminophen 500 mg, 1 or 2 tablets by mouth, every 4–6 hours as needed for pain. Do not take more than 6 tablets in a 24-hour period."
Solicit follow-up questions from the patient or caregiver.	"I really don't like to sit still—can I just keep moving and get through the pain?"

Relevant Evaluation Criteria	Scenario/Model Outcome
	"I buy expensive shoes—are you sure that I am not using the right ones?"
Answer the patient's or caregiver's questions.	"Your active lifestyle is so healthy, especially for someone in your age group, and normally I would encourage you to continue your physical activity. But you are having pain right now, so it probably is best to rest until the symptoms subside. In the meantime, see a podiatrist or other foot care specialist to check your shoes for proper fit or needed cushioning or support. Everyone's feet are different and may exhibit anatomic changes over time. Because of your diabetes, it is especially important to have a podiatrist, who specializes in foot manifestations of chronic diseases, examine your feet and make the most appropriate suggestions for your care."
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Ask Mrs. Martin to contact you if she has any further questions or concerns.

Key: NDKA = No known drug allergies.

Treatment of Tired, Aching Feet and Exercise-Induced Foot Injuries

Treatment Goals

The primary goal in self-treatment for tired, aching feet is to provide additional support and shock absorbance for the feet in order to reduce foot pain and fatigue. Stretching muscles to prevent limitations on daily activities also is important. The goals in self-treatment for exercise-induced foot problems are (1) to relieve any pain, (2) to prevent secondary bacterial infection if the skin is broken, and (3) to institute measures to prevent further injury.

General Treatment Approach

The first measure to avoid tired, aching feet and exercise-induced foot injuries is to choose well-fitted footwear that has sufficient padding and cushioning (Table 44–1). The second is to identify appropriate measures personalized to individual patient needs. For athletes, wearing sport-specific shoes with good arch support (e.g., running shoes) is an excellent measure for preventing heel pain. Persons who are physically active or stand for prolonged periods during the day may need to take additional measures, such as replacing worn shoes or heel pads, using a night splint, strapping or taping the arch, decreasing the amount of weight-bearing activity, and, if necessary, embarking on a weight reduction program.²¹ Oral and topical nonprescription anti-inflammatory agents as well as nonpharmacologic options such as ice applications (Table 44–5) also are appropriate. Magnesium sulfate (Epsom salts) baths have historically been used for soothing tired aching muscles, sprains, and bruising, but no scientific evidence supports these claims. When self-treatment fails, patients should be referred to an appropriate health care provider for evaluation for any bone malalignments and possible orthotic therapy. Figure 44–4 outlines self-treatment for tired, aching feet.

TABLE 44–5 Guidelines for Applying Cold Compresses

Ice Bag Method

- Fill the ice bag with crushed or shaved ice to one half to two thirds of its capacity, if possible. These forms of ice will promote greater contact with the injured body part.
- If necessary, break ice into walnut-sized pieces with no jagged edges. An overfilled bag will be difficult to apply because it will not rest on the contour of the body area.
- After filling the bag, squeeze out trapped air. Then dry the outside of the bag and check for leaks.
- Bind the injured body part with a wet elastic wrap. The wet wrap aids transfer of cold to the injured area.
- If the ankle is being treated, keep it in a dorsiflexed position (foot tipped toward the nose) when it is wrapped in the elastic bandage.
- Apply the ice bag to the specific body part.
- To avoid tissue damage, apply the ice bag for 10 minutes and then remove it for 10 minutes. If the bag is not cloth-covered, wrap the injured area or the ice bag in a thin towel to prevent tissue damage.
- Follow this application regimen 3–4 times a day.
- For most injuries, continue the cryotherapy until swelling decreases or for a maximum of 12–24 hours. Application of ice may be necessary for up to 48–72 hours, depending on the severity of the injury. (For example, the maximum swelling of ankle injuries may occur up to

48 hours after the injury.)

- Before storing the ice bag, drain it and allow it to air dry. If possible, turn it inside out for more efficient drying. Cap the bag and store it in a cool, dry place.

Cold Wraps

- To activate a single-use cold pack, squeeze the middle of the pack to burst the internal bubble. This action initiates an endothermic reaction of ammonium nitrate, water, and special additives.
- For a reusable cold wrap (cold pack or gel pack), store it in the freezer for 2 hours. Do not put the cloth cover in the freezer.
- Remove the cold wrap from the freezer, insert it in the cloth cover, and apply it to the injured body part.
- If the cold wrap is uncomfortable, remove it for 1–2 minutes and then reapply it.
- Alternate application of the cold wrap (10 minutes on, 10 minutes off) 3–4 times a day for 24–48 hours.
- After use, store the cold wrap in the freezer.
- Although some gel packs are nontoxic, keep all cold wraps out of children's reach.

Source: [References 20](#) and [26](#).

Additional measures to prevent exercise-induced injuries entail using suitable footwear that fits properly ([Table 44–1](#)); walking or running on nontraumatizing surfaces; using correct posture (i.e., running erect); and stretching muscles before exercising. Most running injuries can be successfully managed with measures such as shoe modifications and use of shoe inserts or in-shoe supports.

If an injury to the leg or foot occurs, activity usually must be interrupted to allow the injured leg or foot to rest and heal. The health care provider may be called on to play an important role in initial management of an exercise-induced injury to the foot ([Figure 44–5](#)). Identifying the location of the pain will help determine the type and extent of the injury. Establishing the nature and duration of the pain will help ascertain whether self-treatment for the injury is appropriate.

Relative rest (i.e., avoiding activities that produce the symptoms) often is indicated. Alternative exercise such as swimming, rowing, and/or bicycling (stationary or outdoor) should be encouraged. If the injury warrants, the

patient can be instructed on selecting and using nonprescription accessories (e.g., compression bandages, arch supports, heel cushions) and related modalities (e.g., cryotherapy, PRICE [protection, rest, ice, compression, elevation]) that will alleviate injuries or other underlying problems. Systemic analgesics also can relieve the pain and inflammation associated with minor foot injuries (see [Chapter 5](#)).

Nonpharmacologic Therapy

Shoe Inserts, Partial Insoles, and Heel Cups/Cushions

Full-shoe inserts, which can provide cushioning and absorb shock, are available in various sizes and thicknesses to accommodate the needs of most patients with exercise-related foot problems. Such inserts help decrease the incidence of lower back pain associated with the impact from walking. The selected insert should conform to the type of shoe worn.^{7,8}

Partial insoles are preferred when the patient needs cushioning or support in a certain portion of the shoe. For example, metatarsal arch supports, which fit into the ball-of-foot region of the shoe, help lift the arch behind the toes to alleviate pain associated with the spreading of the foot, a condition that occurs with increasing age in women. Inserts specifically designed to fit in high-heeled shoes (e.g., Dr. Scholl's for Her High Heel Insoles) also are available. Finally, the arch support insert is intended to cushion and support painful arches.^{9,13}

Use of a heel cup or heel cushion may be indicated, depending on the location and extent of the pain. For example, a heel cushion might be appropriate when the pain is confined to the bottom of the heel. A heel cushion supports the entire heel as it elevates the sensitive area to prevent further irritation. Alternatively, when the pain is widespread and diffuse, a heel cup might be more appropriate. Heel cups help relieve the pain caused by physiologically mediated breakdown of the heel's natural padding or by intense athletic activity.

Caution is warranted in the selection of shoe inserts. If an insole added for needed cushioning affects the gait, the patient should be referred to a podiatrist or pedorthist; the latter specializes in the designing, manufacturing, modifying, and fitting of footwear and orthotics. Insoles should be used only to

cushion the foot, not to correct malformation, which requires a specialist's attention.

Athletic Footwear

Appropriate footwear can be a powerful tool for manipulating human movement and can greatly influence the healing of injured tissues, both positively and negatively. A study focusing on the stresses incurred by runners' feet demonstrated that the type of footwear chosen by recreational runners is important in preventing injury, specifically highlighting the benefit of stride-neutral shoes or motion-controlled footwear.²⁰ It follows that inappropriate or worn-out shoes can result in foot injuries and pain. Athletic shoes should be replaced after 200–400 miles of use.²¹

Compression Stockings

Compression stockings also are an option to enhance support for people who spend many hours on their feet. Compression stockings may be purchased with or without a prescription in compressions ranging from 8 to 30 mm Hg. These stockings decrease inflammation by improving circulation, thereby reducing fatigue of the feet, legs, and back.^{22,23}

Compression Bandages

Typically, a compression bandage (e.g., Ace Bandage) is used to support a sprained ankle or knee. If a compression bandage is to be used, the width of the bandage depends on the injury site. For example, a foot or an ankle requires a 2- to 3-inch bandage.²⁴ **Table 44–6** describes the proper method of applying this type of bandage.

TABLE 44–6 Application Guidelines for Compression Bandages

- Choose the appropriate size of bandage for the injured body part. If you are unsure about the size, purchase a product designed for the appropriate body part.
- Recommended elastic bandage width for coverage area:
 - 2 inches: foot, wrist, ankle
 - 3 inches: elbow, knee, ankle
 - 4 inches: knee, lower leg, shoulder
 - 6 inches: shoulder, upper leg, chest

- Unwind approximately 12–18 inches of bandage at a time and allow the bandage to relax.
- If ice also is being applied to the injured area, soak the bandage in water to aid the transfer of cold.
- Wrap the injured area by overlapping the previous layer of bandage by approximately one third to one half of its width.
- Snugly wrap the point most distal from the injury. For example, if the ankle is injured, begin wrapping just above the toes.
- Decrease the tightness of the bandage as you continue to wrap. (Follow package directions on how far to extend the bandage past the injury.) If the bandage feels tight or uncomfortable or if circulation is impaired, remove the compression bandage and rewrap it. Cold or swollen toes and fingers indicate that the bandage is too tight.
- After using the bandage, wash it in lukewarm, soapy water; do not scrub it. Rinse the bandage thoroughly, and allow it to air-dry on a flat surface. Roll up the bandage to prevent wrinkles, and store it in a cool, dry place. Do not iron the bandage to remove wrinkles.

Source: [Reference 27](#).

Cryotherapy

Applying cold compresses to an injury, such as a muscle sprain, provides a local anesthetic effect and decreases pain and inflammation. Ice bags or cold wraps are useful for cold application in 10-minute increments. [Table 44–5](#) describes the proper method of cold application to injuries.

Contrast Bath Soaks

For acute injury, cold application is beneficial during the first 48 hours to decrease ensuing inflammation. Specifically, the cold therapy is intended to decrease inflammation. Subsequent warm therapy attempts to bring increased blood flow to the affected area and to facilitate smooth muscle relaxation.

Algorithm: Tired, Aching Feet

FIGURE 44–4 Self-care for tired, aching feet.

Algorithm: Exercise-Induced Injuries

FIGURE 44–5 Self-care for exercise-induced injuries. Key: PRICE = Protection, rest, ice, compression, elevation; RICE = rest, ice, compression, elevation.

Patient Counseling and Evaluation of Patient Outcomes for Tired, Aching Feet and Exercise-Induced Injuries

Recommendations to resolve pain in the soles or heels of the feet depend on whether the patient has exclusions for self-treatment and how long the foot problem has persisted. Follow-up evaluation is indicated after 1 week to determine whether the treatment recommendations, such as the use of new shoes and/or in-shoe supports, compression bandages, or cryotherapy or other anti-inflammatory therapy, have reduced or eliminated the discomfort. If the initial swelling and/or pain persist, medical referral is warranted. Depending on the acuity of the symptoms, patients should consult their primary care provider (for exercise-induced injuries) or podiatrist for an appropriate evaluation. The boxes “Patient Education for Tired, Aching Feet” and “Patient Education for Exercise-Induced Injuries” detail the patient counseling that should be provided along with indications for seeking medical attention.

Ingrown Toenails

The most frequent cause of ingrown toenail, or *onychocryptosis*, is incorrect trimming of the nails. The correct method is to cut the nail straight across without tapering the corners. Wearing pointed-toe or tight shoes or too-tight hosiery also has been implicated. Other causes and contributing factors are hyperhidrosis, trauma, obesity, and excessive pressure on the toes. Direct pressure on a toe can force the lateral or medial edge of the nail into the soft tissue. The embedded nail may then continue to grow, resulting in swelling and inflammation of the nail fold.^{21,25,26}

Bedridden patients are at increased risk for development of ingrown toenails from the pressure of tightly “tucked” or heavy bedcovers on the soft skin tissue against the nails. Other potential causes of ingrown toenails include nail curling, which can be hereditary or secondary to incorrect nail trimming; onychomycosis; or a systemic metabolic disease.

Pathophysiology of Ingrown Toenails

An ingrown toenail occurs when the nail curves and becomes embedded into the flesh at the corner(s) of a toe, causing pain (Figure 44–6). Puncture of the skin that is accompanied by soft tissue hypertrophy and subsequent invasion by opportunistic resident foot bacteria can lead to superficial infection. Swelling, inflammation, and ulceration are secondary complications that can accompany an ingrown toenail.²¹

FIGURE 44–6 Bunion and ingrown toenail.

Patient Education for Tired, Aching Feet

The objectives of self-treatment are (1) to reduce impact on the feet by providing additional support and shock absorbance and (2) to relieve foot discomfort. For most patients, carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

- To reduce friction of the feet and impact on weight-bearing parts of the feet, wear well-fitted footwear that has sufficient padding and cushioning (Table 44–1).
- Consider other measures to further reduce impact on the feet, such as decreasing the length of time spent standing or exercising, switching to exercises that have less impact on the feet, and, if necessary, losing weight.
- To relieve swelling or discomfort, apply an ice bag or cold wrap to the affected area (Table 44–5).
- For acute pain relief, NSAIDs such as ibuprofen or naproxen may be

used. [Chapter 5](#) discusses these agents in more detail.

- To improve circulation, select a compression stocking with mild to moderate compression (<20 mm Hg).
- Choose a full-shoe insert when the entire foot aches. Make sure the insert conforms to the shoe. For example, choose a thin insole for a woman's pump and a thicker insole for an athletic shoe.
- Use partial insoles to cushion or support a certain portion of the foot, such as the ball of the foot, the arch, or the toes.
- Use a heel cushion for pain confined to the bottom of the heel.
- Use a heel cup when the heel pain is widespread and diffuse.

When to Seek Medical Attention

- If discomfort or swelling continues after 1 week of implementing appropriate self-care measures, consult an appropriate health care provider.

Key: NSAID = Nonsteroidal anti-inflammatory drug.

Patient Education for Exercise-Induced Injuries

The objectives of self-treatment are (1) to rest the injured foot or limb to allow healing, (2) to relieve discomfort, and (3) to implement measures to prevent further injury. For most patients, carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes.

General Measures

- When a leg or foot injury occurs, rest the injured limb. If desired, perform other types of exercise that do not put a great deal of force on the feet, such as swimming or bicycling (stationary or outdoor).
- The following measures will help prevent exercise-induced injuries:
 - Stretch muscles before exercising.
 - Choose sport-specific shoes with good arch support for

athletic activities.

- Run or walk on a relatively smooth, level, and resilient surface.
- Keep the back straight when running.

Shin Splints

- Rest the feet and apply an ice bag or a cold wrap to the painful area (Table 44–5).
- If desired, take aspirin or another NSAID to relieve pain and reduce tissue inflammation.
- Do not use analgesics before a workout to suppress pain or to increase your endurance.

When to Seek Medical Attention

- Seek medical attention if the discomfort becomes a cramping, burning tightness that repeatedly occurs at the same distance or time during a run.

Blisters

- To prevent blisters during walking or running, wear moisture-wicking socks (e.g., wool or acrylic). If desired, wear two pairs of socks with ordinary talcum powder sprinkled between them. Using an acrylic sock next to the skin will assist in drawing moisture from the foot.
- Apply compound tincture of benzoin or a flexible collodion product (e.g., New Skin) to the blister before exercise to decrease pain and accelerate healing by promoting reepithelialization.
- Apply an antiperspirant that contains aluminum chloride 20% to the feet to decrease incidence of blisters.
- If blisters break, apply a first aid antibiotic to the broken skin to prevent secondary bacterial infection.
- Cover blistered area with moleskin to protect the surface.

Ankle Sprains

- Although maximum swelling will not occur for 48 hours, begin treatment as soon as possible.
- Stay off the injured foot, wrap a compression bandage around the ankle, apply ice, and elevate the affected foot. (Tables 44–5 and 44–6 provide guidelines on applying ice and compression bandages, respectively.)

When to Seek Medical Attention

- Seek medical attention if swelling persists more than 72 hours.

Toenail Blisters/Loss

- To prevent blisters under the toenail, keep toenails trimmed and wear only properly fitted shoes.
- Should a blister develop, do not disturb or puncture the blister roof.

When to Seek Medical Attention

- If the toenail separates from the skin or is lost, consult your primary care provider or a podiatrist for proper treatment.

Key: NSAID = Nonsteroidal anti-inflammatory drug

Treatment of Ingrown Toenails

Treatment Goals

The goals of self-treatment for ingrown toenails are (1) to relieve pressure on the affected nail, (2) to relieve pain, (3) to prevent recurrence of the disorder, and (4) to prevent infection.

General Treatment Approach

Patient education is the best means of preventing the development of ingrown toenails. In the early stages of development, therapy is directed at providing adequate room for the nail to resume its normal position adjacent to soft tissue. This therapy is accomplished by relieving the external source of

pressure. Warm water soaks for 10–20 minutes several times a day until resolution will help soften the area. Topical antiseptics prescribed by a primary care provider can be applied to prevent possible opportunistic infections. Insertion of small cotton wisps or dental floss under the impinged nail edge is associated with a 79% rate of symptomatic improvement. No evidence is linked to secondary infection from the cotton wisps or dental floss.²⁷ Medical referral is necessary if the condition is recurrent or gives rise to an oozing discharge, significant pain, or severe inflammation. Sometimes surgery is warranted; with subsequent systemic antibiotic therapy, the toe may take up to 3–4 weeks to heal. The most common surgical procedure is removal of the lateral edge of the nail followed by chemical matricectomy achieved by phenolization. This process destroys the exposed nail-forming matrix.^{21,26} Figure 44–7 outlines self-treatment options for ingrown toenails.²⁰

Pharmacologic Therapy

Sodium Sulfide Gel and Nonsteroidal Anti-inflammatory Drugs

Sodium sulfide 1% gel is applied topically, and a retainer ring is placed around the affected area to help maintain the product at the site of action. Sodium sulfide relieves pain by softening the nail or by hardening the nail bed. For relief of ingrown toenail discomfort, sodium sulfide may be applied twice daily for up to 7 days.^{28,29} Health care providers must be aware of misleading trade-name products marketed for ingrown toenails and educate patients accordingly. Products containing benzocaine 20% relieve pain associated with ingrown toenails, but this agent does not treat the underlying problem.^{27,29–31} Oral nonsteroidal anti-inflammatory drugs (NSAIDs), such as oral aspirin, ibuprofen, or naproxen, may be recommended in the absence of contraindications (Chapter 5).

Algorithm: Ingrown Toenail

FIGURE 44–7 Self-care for ingrown toenail. Key: NSAID = Nonsteroidal anti-inflammatory drug.

Assessment of Ingrown Toenail: A Case-Based

Approach

The pharmacist as health care provider can play a vital role in recommending measures for relieving acute pain from ingrown toenails and in preventing their recurrence. For clinical management of this condition, initial recommendations include warm bath soaks to soften the skin and oral anti-inflammatory therapy for temporary pain relief. If the toenail or nail bed is infected, immediate referral for medical care is warranted.

Patient Counseling for Ingrown Toenails

The box “Patient Education for Ingrown Toenails” lists specific information to include in patient counseling.

Evaluation of Patient Outcomes for Ingrown Toenails

Patient reevaluation after 3–4 weeks is indicated to determine whether pressure relief and preventive measures have been successful. Medical referral is appropriate if the condition shows no improvement or worsens or if a discharge from the site of irritation is noted.

Patient Education for Ingrown Toenails

The ultimate goals for self-treatment for ingrown toenails are (1) to relieve the pain and pressure associated with the condition and (2) to prevent recurrence.

- Ensure that shoes fit properly to eliminate pressure on the toenails (Table 44–1).
- Prevent recurrence of ingrown toenails by cutting nails straight

across, rather than at an angle or in a curve.

- Decrease pain and swelling of the ingrown toenail by taking an NSAID such as ibuprofen or naproxen.
- Relieve impingement of the nail by soaking the affected foot in warm water to soften the nail and the skin around it.
- Place cotton wisps or dental floss under the edge of the ingrown nail for almost immediate pain relief.

Key: NSAID = Nonsteroidal anti-inflammatory drug.

Key Points for Foot Disorders

- Foot pain is not normal and therefore should be evaluated by the health care provider as for any other health care complaint.
- Patients with diabetes, circulatory problems, and/or arthritis should be referred for further medical evaluation before implementing use of any nonprescription topical or oral medication.
- Nonprescription products may exacerbate certain conditions; the health care provider must monitor patient progress carefully and be attuned to patient comments that might indicate the occurrence of drug-related problems.
- The nonprescription drug of choice to treat corns and calluses is salicylic acid in a collodion-like vehicle or plaster form. Additionally, predisposing factors responsible for corns and calluses must be corrected.
- Patients also should be cautioned that frequent recurrence of any of these foot disorders is an indication to consult a podiatrist or primary care provider.
- Health care providers should be prepared to provide management recommendations for patients who present with

various exercise-induced injuries.

- Some exercise-induced injuries can be successfully managed with shoe modifications, use of in-shoe supports, modified training methods, ice applications, and stretching exercises. It is important for athletes to recognize and seek treatment for foot pain.
- Counseling on proper foot hygiene is an important aspect of whole-patient care.

Chapter 45: Hair Loss

Authors: Tricia M. Berry

A significant number of men and women experience hair loss. Up to 80% of white men and 40%–50% of white women are affected at some point in their lives, and white men are more likely to experience hair loss than men of other ethnicities.¹ Many potential contributing factors for hair loss are recognized (Table 45–1).^{2–10} Regardless of the cause, hair loss can have a significant psychological and social impact. People affected by hair loss often experience low self-esteem; personal, social, and work-related challenges; and psychiatric disorders, such as depression and anxiety.¹¹ The economic impact also is substantial, with patients spending approximately \$3.5 billion each year on products and procedures to combat hair loss.¹²

TABLE 45–1 Causes of Hair Loss	
Etiologic Category	Specific Examples
Hormonal changes	Hyperandrogenic conditions (e.g., polycystic ovary syndrome)
	Menopause
	Postpartum period
Physiologic stress	Fever, infections
	Hemorrhage
	Surgery
	Trauma
Chronic illnesses	Autoimmune diseases (e.g., rheumatoid arthritis, lupus)
	Eating disorders (e.g., anorexia, bulimia)
	Endocrine disorders (e.g., hypothyroidism/hyperthyroidism, hypopituitarism, diabetes mellitus, metabolic syndrome, hyperprolactinemia)
	Hepatic or renal failure

Etiologic Category	Specific Examples
	Infections (e.g., HIV infection, syphilis)
Medications	ACE inhibitors (e.g., enalapril, captopril)
	Allopurinol
	Androgenic action (e.g., oral contraceptives, danazol, testosterone, anabolic steroids)
	Anticonvulsants (e.g., phenytoin, carbamazepine, valproate)
	Anticoagulants (e.g., warfarin, heparin)
	Antidepressants (e.g., SSRIs, tricyclic antidepressants)
	Beta blockers (e.g., propranolol, metoprolol)
	Cholesterol-lowering drugs (e.g., clofibrate, gemfibrozil)
	Chemotherapeutic agents
Dietary changes or deficiencies	Protein restriction/deficiency
	Rapid weight loss including that associated with bariatric surgery
	Strict vegetarian diet
	Zinc, biotin, or iron deficiency
Local trauma	Hair care practices
	Tinea capitis
	Trichotillomania (compulsive hair plucking)
Genetics	Chromosomal loci 3q26 and 20p11 in AGA ⁹
	HLA alleles, such as HLA-DRB1*0401 and DQB1*0301, in alopecia areata ⁷
	Polymorphisms in the androgen receptor gene in AGA ^{8,9}

Key: ACE = Angiotensin-converting enzyme; AGA = androgenetic alopecia; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; SSRIs = selective

serotonin reuptake inhibitors.

Source: [References 2–10](#).

Hair loss is broadly categorized as either nonscarring or scarring alopecia. Forms of nonscarring alopecia include *androgenetic alopecia* (AGA), or hereditary pattern hair loss; *alopecia areata* (rapid-onset, patchy hair loss); *anagen effluvium* (rapid shedding of growing hairs); *telogen effluvium* (rapid shedding of resting hairs); cosmetic hair damage; *trichotillomania* (a compulsive pulling out of one's hair); and tinea capitis (fungal infection/ringworm of the scalp). Types of hair loss secondary to medication use, acute or chronic illness, or dietary changes typically also are nonscarring. [Table 45–2](#) provides information on common types of nonscarring alopecia.^{1,3,5–8}

TABLE 45–2 Characteristics of Common Types of Nonscarring Alopecia

Type of Hair Loss	Etiology	Epidemiology	Clinical Presentation
Androgenetic alopecia/ hereditary pattern hair loss	Hormonal, hereditary	<i>Female:</i> 40%–50% affected by age 70 years ^{1,7}	Gradual onset with progression of gender-specific pattern hair loss
		<i>Male:</i> 80% affected by age 70 years ¹	<i>Female:</i> Central portion of scalp, sparing frontal hairline; wide midline part on the crown with progression to diffuse thinning over crown
		Affects white men more often than men of other ethnicities ¹	<i>Male:</i> Top rear of the head (vertex), frontal hairline, and occipital regions
Alopecia areata	Autoimmune	2% of U.S. population; affects men and women of all races equally; most cases (70%)	Abrupt onset (may wax and wane with relapses); usually patchy but can be generalized; can occur in any hair-bearing area; can progress to complete loss of scalp hair (alopecia totalis) or total loss of body hair

Type of Hair Loss	Etiology	Epidemiology	Clinical Presentation
		occur in children and young adults ⁸	(alopecia universalis)
Anagen effluvium	Chemotherapy, radiation therapy, heavy metal poisoning	Data not available	Abrupt, diffuse loss of hair within days of exposure
Telogen effluvium	Metabolic or hormonal disturbances, stress; severe illness or injury; medications	Exact prevalence unknown; can occur in either gender at any age	Diffuse, abrupt onset (often several months after trigger exposure); rapid hair thinning (e.g., clumps of hair loss)
Cosmetic hair damage ^a	Hair care practices (e.g., braiding, permanent waving, bleaching)	Any age; associated with specific social, cultural, and cosmetic practices	Gradual or abrupt loss on any area of the scalp depending on cause; broken hairs with blunt rather than tapered tips
Trichotillomania	Psychiatric compulsive disorder	More common in children but may persist into adulthood	Twisted and broken-off hairs visible in patchy areas across the scalp
Tinea capitis ^a	<i>Trichophyton tonsurans</i> infection	Any age; common in childhood	Any area of the scalp; usually round patch(es) of hair loss

^a In rare circumstances, chronic and/or severe cases can lead to scarring alopecia.

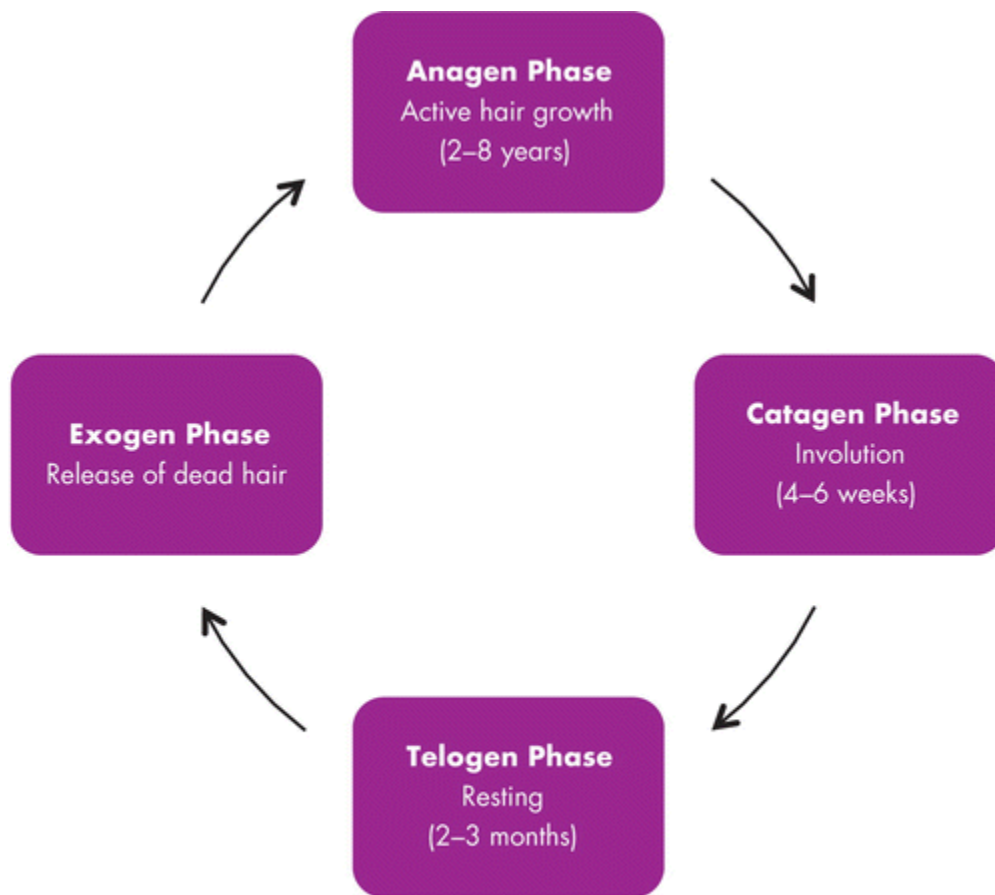
Source: [References 1, 3, and 5–8](#).

Scarring alopecia may be related to conditions such as discoid lupus erythematosus, syphilis, sarcoidosis, or lichen planus. Severe forms of tinea capitis and chronic hair care practices (e.g., braiding, permanent waving) that can significantly damage the hair and scalp also may lead to scarring alopecia.

AGA is the most common form of hair loss and the only type of alopecia for which U.S. Food and Drug Administration (FDA)– approved nonprescription medications are available. AGA is characterized by progressive, male or female pattern hair loss from the scalp.

Pathophysiology of Hair Loss

Hair follicle activity is cyclic ([Figure 45–1](#)). A variety of triggers can alter the hair follicle cycle, resulting in hair loss.



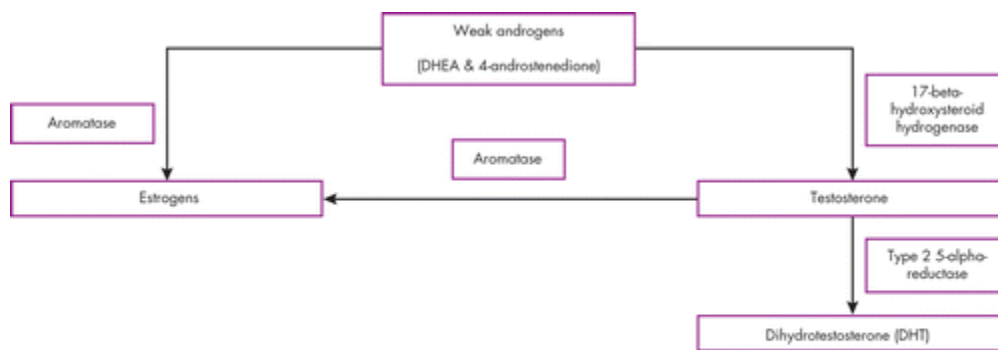
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FIGURE 45–1 Normal hair follicle cycle.

In AGA, the hair follicle undergoes a stepwise literal miniaturization and change in growth dynamics. With each successive cycle, the anagen phase (active growth) becomes shorter and the telogen phase (resting phase)

becomes longer. Consequently, over time, the anagen–telogen ratio decreases from 12:1 to 5:1. Because telogen hairs are more loosely anchored to follicles, their presence in increased numbers eventually leads to increased shedding. In addition, the catagen phase lengthens, reducing the number of hairs. As telogen hairs are shed, they are gradually replaced by *vellus-like* (short and very fine) hairs or by anagen hairs that are too short to reach the surface.

Hair follicles and their sebaceous glands produce enzymes that convert weak androgens to estrogens, testosterone, and dihydrotestosterone (DHT) (Figure 45–2). These enzymes are believed to maintain androgen balance in the follicle, thereby regulating the hair cycle.



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FIGURE 45–2 Androgen metabolism within the hair follicle. Key: DHEA = Dehydroepiandrosterone.

DHT is thought to be a primary repressor of hair growth. It binds 5 times more readily than testosterone to androgen receptors. Increased 5-alpha-reductase–mediated conversion of testosterone to DHT in the affected areas in women with AGA also supports the contention that DHT is important in this process. In contrast with men, women with AGA rarely lose all their hair, not only because they have less 5-alpha-reductase but also because they have more aromatase. The excess aromatase converts testosterone into estradiol, thereby reducing the level of androgen and increasing the estrogen level.¹³ In addition, hair follicles in women typically have fewer localized androgen receptors, so retention of actively growing hair is more likely.¹⁴

Although the pathomechanisms are not fully understood, alopecia areata is thought to have an autoimmune etiology and genetic influences.⁸

Chemotherapeutic agents (e.g., antimitotic drugs) are identified as a potential cause of anagen effluvium. Their physiologic effects include narrowing of the hair shaft, which may fracture the hair or stop hair growth. See [Table 45–1](#) for additional medications that may cause hair loss.

Certain triggers (e.g., severe illness, injury, stress, metabolic changes, thyroid disorders, autoimmune disorders) may precipitate telogen effluvium, which occurs when an increased number of hairs shift from the anagen phase to telogen phase. Nutritional deficiencies, particularly iron deficiency, also can cause hair loss.

Hair care products and hair-grooming methods potentially associated with microtrauma or burns to the scalp may result in scarring alopecia. *Traction alopecia* is seen primarily in persons who braid their hair tightly every day. Braiding traumatizes the hair follicles, causing hairs to loosen and break. Use of oily moisturizers to make hair more manageable and to stop the scalp from flaking may lead to development of folliculitis with consequent hair loss.

Psychological stress may potentiate several types of hair loss, although the literature on this subject is conflicting. Trichotillomania, a compulsive psychiatric disorder most common in children, involves repetitive pulling out or plucking of hairs, leading to patchy hair loss.

Untreated or improperly treated tinea capitis may lead to hair loss. Treatment for this condition requires a regimen of prescription systemic antifungals; hair regrowth occurs after eradication of the causative dermatophyte.

Scaly dermatoses (e.g., psoriasis, seborrheic dermatitis) also may lead to scarring alopecia. Nonprescription agents marketed for the treatment of psoriasis and seborrheic dermatitis are not effective in treating alopecia. [Chapter 34](#) provides additional information on self-care for scaly dermatoses.

Clinical Presentation of Hair Loss

The scalp of a patient with AGA shows no signs of inflammation or scarring. Hair loss is gradual; in contrast with the clinical picture in other types of alopecia, the number of hairs that come out during brushing or shampooing does not suddenly increase. Typically, male pattern hair loss (MPHL) starts at

some point after puberty and is insidious in onset. Progression fluctuates considerably, with 3–6 months of accelerated loss followed by 6–18 months of no loss, with subsequent resumption of this sequence. In most affected men, the hair loss occurs over a period of 15–25 years. MPHL begins with a recession of the frontal hairline and continues with thinning at the vertex until only a fringe of hair at the occipital and temporal margins remains. The pattern and extent of hair loss in this condition often are characterized using the Norwood Scale; images are viewable at the referenced website.¹⁵

In women with alopecia, hair loss typically is more diffuse. Female pattern hair loss (FPHL) manifests as gradual hair thinning over the crown and midfrontal portion of the scalp. Several scales (e.g., Ludwig, Sinclair, Savin) have been used to classify the extent of FPHL; the relevant images can be viewed at the referenced website.^{4,16} Such scales are helpful in visualizing the typical progression of hair loss in MPHL (Norwood) and FPHL (Ludwig, Sinclair, Savin), assessing the patient's pattern of hair loss as MPHL or FPHL, and evaluating appropriateness of a self-care approach.

FPHL, also classified as AGA, is attributed to genetic components along with hormonal factors.^{9,17} Women with AGA may present with signs and symptoms of *hyperandrogenism* (an excess of androgen), such as significant acne; *hirsutism* (hairiness in other parts of the body); menstrual irregularities; and infertility. It is conceivable that a patient with FPHL may be using a hair regrowth treatment agent on the scalp while also using an antihirsutism agent (e.g., topical eflornithine, oral spironolactone [off label]) to remove excess hair on the face. Androgen excess may indicate serious metabolic disturbances, such as cardiovascular disease, diabetes mellitus, polycystic ovary syndrome, and endometrial cancer.¹⁷ Women with multiple signs and symptoms should be referred for medical evaluation and treatment.^{9,17}

Alopecia areata occurs in three stages: sudden loss of hair in patches, enlargement of the patches, and regrowth. This cycle may take months or sometimes years, and any hair-bearing area may be affected. Up to 5% of patients lose all of the scalp hair (*alopecia totalis*), and 1% of patients lose all body and scalp hair, including eyebrows and eyelashes (*alopecia universalis*).³ Hair loss may accompany or be preceded by nail pitting or other nail abnormalities. Itching, tingling, burning, or other painful sensations also may be experienced in the patch of hair loss.

Telogen effluvium (also known as diffuse alopecia) can be acute (lasting <6

months) or chronic (lasting >6 months). The precipitating factor usually precedes shedding by 1–6 months, but identifying a specific causal event often is difficult, if not impossible. This point is especially relevant with medication use in that hair loss often will occur up to several months after initiation of a particular drug therapy. The health care provider should ascertain the start date of all medications as a part of the clinical workup for patients with telogen effluvium. This type of hair loss usually is reversible.^{2,3,5}

Hair loss may be assessed by using a variety of tests (e.g., biopsy of the scalp, daily hair loss count, hair-pull test).^{2,3} A *hair-pull test* is done by holding 40–60 hairs between the thumb and forefinger and firmly (but not forcefully) pulling the hairs away from the scalp. A positive test result, in which more than 10% of the hairs are removed, suggests types of alopecia other than AGA (e.g., effluvium, alopecia areata).³ All patients presenting with hair loss that is not considered androgenic should be referred to an appropriate health care provider for complete medical evaluation.

Treatment of Hair Loss

Treatment Goals

The goal in self-treatment for hair loss is to achieve an appearance that the patient considers acceptable with a corresponding decrease in the emotional distress experienced.

General Treatment Approach

If a self-treatment approach to hair loss is appropriate, the treatment objectives can be accomplished through nonprescription measures consisting of nonpharmacologic strategies such as cosmetic camouflage and/or the use of topical minoxidil to stimulate hair growth, if applicable. With the exception of AGA, all other types of hair loss should be referred for medical evaluation to determine the cause and proper treatment. The algorithm in [Figure 45–3](#) outlines the self-care approach to management of hair loss, with a list of specific exclusions for self-treatment.

Nonpharmacologic Therapy

Hair loss can be psychologically damaging. Camouflaging thinning hair with wigs and hair weaves may help relieve the associated emotional distress. Technological advances have made production of custom wigs that match the wearer's original hair a standard practice. Approaches to treating less severe hair loss include use of hair sprays, gels, colorants, permanents, and scalp-camouflaging products (e.g., topical hair fibers, powder cakes, scalp lotions, scalp sprays, hair crayons). Such products can create an illusion of fullness; they do not actually decrease hair loss.^{1,18}

Scalp massage, frequent shampooing, and electrical stimulation have been proposed as treatments for hair loss; however, these remedies are considered ineffective.¹⁹ Although data regarding its efficacy are inconsistent, low-level light therapy is FDA approved and marketed for hair growth.^{1,17,20,21}

If hair loss is caused by poor diet or iron deficiency, the patient may benefit from consultation with a dietitian. In iron deficiency states, increasing protein intake or taking iron supplements may be a simple solution, with subsequent reversal of hair loss.

Surgical transplantation of terminal hair follicles from another anatomic site is an alternative nonpharmacologic approach to hair loss (e.g., hair follicles from the occipital region may be implanted to the frontal and vertex scalp).²¹

Pharmacologic Therapy

Minoxidil

Minoxidil, the only FDA-approved agent for self-treatment for AGA, is available as 2% and 5% hydroalcoholic solutions and as a 5% solvent-free foam. Minoxidil can be applied by various methods ([Table 45–3](#)), depending on the applicator (i.e., spray, dropper).²² This treatment is indicated for AGA involving the scalp.²² Specifically, nonprescription topical minoxidil is labeled for baldness at the crown of the head in men and for hair thinning in the frontoparietal area in women. The 2% and 5% solutions (1 mL twice daily) and 5% foam (½ capful twice daily) are approved for use in men, whereas only the 2% solution (1 mL twice daily) and 5% foam products (½ capful once daily) are approved for use in women.²² When used orally to control hypertension, minoxidil is a potassium

channel opener and vasodilator. When used topically for hair loss, the drug appears to increase cutaneous blood flow, promote and maintain vascularization of hair follicles, directly stimulate follicular hypertrophy, and prolong the anagen phase. Minoxidil also may transform resting (*telogen phase*) hair follicles into active (*anagen phase*) hair follicles, resulting in a lower percentage of hairs in the telogen phase, which are shed more easily.^{23–25} It is proposed that minoxidil enhances hair growth by stimulating prostaglandin endoperoxide synthase-1, leading to increased production of prostaglandin E₂, which results in prolonged anagen phase.^{5,21,26}

TABLE 45–3 Administration Guidelines for Nonprescription Minoxidil

Minoxidil Solution

- Apply minoxidil to clean, dry scalp and hair.
- Rub about 1 mL of the product into the affected area of the scalp. Some products have a measuring cap with a 1-mL fill line. Do not apply the product more often than twice daily (morning and night).
- Wash and dry hands after applying the medication. If it gets into the eyes, mouth, or nose, rinse these areas thoroughly with tap water.
- Do not double the dose if you miss an application.
- Allow 2–4 hours for the drug to penetrate the scalp. Do not participate in any activity that might wash away or dilute the drug (e.g., bathing or swimming without a cap) for 2–4 hours after application.
- At night, apply the drug 2–4 hours before bedtime; if the product is not allowed to dry completely, minoxidil can stain clothing and bed linen.
- A hair dryer, on a low setting, may be used after applying the drug to speed drying of the hair.
- If applicable, apply hair grooming and styling products (e.g., sprays, mousses, gels) after the minoxidil has dried. These products usually do not affect the efficacy of topical minoxidil.
- Avoid using topical minoxidil on the day of and for 24 hours after using permanent wave or hair color products, to reduce scalp irritation.

Minoxidil Foam

- The foam may “melt” on contact with warm skin. Therefore, wash hands in cold water and dry them thoroughly before applying foam.
- Within the thinning hair area, part the hair into one or more rows to maximize contact of the foam with the scalp. The hair should be completely dry before application.
- Holding the product can upside down, apply ½ capful of the foam to the fingertips. The 5% product for men should be applied twice daily, in the morning and at night. The 5% product for women should be applied once daily.
- Using the fingertips, spread the foam over the thinning scalp area, and then massage gently into the scalp. Wash hands thoroughly after application.

- Allow the product to dry completely before lying down or applying grooming/styling products.
- Avoid using topical minoxidil on the day of and for 24 hours after using permanent wave or hair color products, to reduce scalp irritation.

Source: [References 22](#) and [28](#).

For men undergoing hair transplantation whose hair follicles may be viable but not functioning optimally in the area to be transplanted, topical minoxidil can increase hair density, speed regrowth in transplanted follicles and also can complement the surgical outcome by minimizing the likelihood of progression of hair loss.²⁷

After initiation of minoxidil treatment, an increase in hair loss may occur within the first few weeks of product usage.²⁸ Several months may elapse before hair growth is apparent. If increased hair density fails to appear after 4–6 months of minoxidil use, the patient should consider discussing other options with the treating health care provider.^{22,28} In many cases, increased hair density is minimal, and treatment response is difficult to assess. Once the drug is discontinued, hair density returns to pretreatment levels in a matter of months; therefore, the patient must continue to use the product indefinitely to maintain new growth.²²

Several studies have evaluated the safety and effectiveness of topical minoxidil 2% and 5% preparations. In a 48-week study, men using 5% minoxidil showed greater benefit, in terms of earlier response and increased hair regrowth (i.e., 45% more), than that seen in men using 2% minoxidil.²⁹ Of note, however, increased frequency of itching and local irritation also was noted in the 5% minoxidil treatment group compared with the 2% minoxidil group.²⁹ A randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of 5% topical minoxidil compared with those of 2% topical minoxidil and placebo in the treatment of FPHL.³⁰ Both 5% and 2% preparations of minoxidil were superior to placebo, and the 5% topical minoxidil group showed statistically significant benefits over the 2% topical minoxidil group.³⁰ The incidence of itching, local irritation, and *hypertrichosis* (excessive hair growth)

in the group receiving 5% minoxidil was greater than that in the 2% minoxidil and placebo groups.³⁰ In a randomized, single-blind trial studying 113 women with AGA, once-daily 5% minoxidil foam was found to be as effective as twice-daily 2% minoxidil solution; the 5% concentration also was associated with several aesthetic and practical advantages (e.g., once-daily administration; lower rates of adverse effects, such as itching and dandruff; less interference with hair styling).³¹

Some patients who require prescription treatment with finasteride may still use topical minoxidil for an adjunct therapy. Topical minoxidil solution 2% has been investigated in combination with oral finasteride 1 mg in male patients. The outcomes of this study indicate a higher percentage of responders with the combination treatment than with either agent alone.³²

The most common adverse effects associated with minoxidil—local itching, irritation, and dryness or scaling at the site of application—may be related to the hydroalcoholic/propylene glycol vehicle in the product used. Use of the 5% minoxidil topical formulation in a propylene glycol-free foam vehicle reduces the risk of local adverse effects.

Transient hypertrichosis, usually on the forehead and cheeks, is a possible adverse effect with long-term use of minoxidil. Occasionally, patients may notice hypertrichosis on the chest, back, forearms, and ear rims, which could indicate that the product has been applied excessively.³³ Rare adverse effects include acne at the site of application, increased hair loss, inflammation (with soreness) of the hair roots, reddened skin, swelling of the face, and allergic contact dermatitis.^{22,28}

Minoxidil is absorbed through the skin in relatively low concentrations; documented systemic adverse effects are rare. In the unlikely event of an accidental ingestion, the patient should seek emergency medical attention or contact a poison control center.

Although minoxidil-induced hemodynamic changes have not been detected in most controlled clinical studies, patients with preexisting cardiovascular disorders may be at increased risk for adverse cardiovascular effects (e.g., chest pain, dizziness, fainting, tachycardia).³⁴

Researchers have found little evidence of a potential effect of minoxidil on systemic endocrine functions.³⁵ Measurement of plasma testosterone and

excretion of urinary hydroxysteroids and ketosteroids in hypertensive patients who had been treated with oral minoxidil did not reveal any effects. In a study of topical minoxidil, however, the modification of follicular testosterone metabolism occurred despite unchanged serum cortisol, testosterone, and thyroid indices.³⁶

The use of topical minoxidil is not associated with any known drug–drug interactions. Topical application of corticosteroids, petrolatum, or retinoids (e.g., adapalene, tretinoin) to the scalp in combination with minoxidil should be avoided because of possible increased absorption of minoxidil and increased risk of adverse effects. In addition, minoxidil should not be used for 24 hours before or after application of any hair permanent, hair color, or hair relaxant products.^{22,28}

Patients who are allergic to minoxidil or to any component of the preparation should avoid this medication. Patients with scalp damage from psoriasis, severe sunburn, or abrasions should also avoid topical minoxidil; these conditions may increase minoxidil absorption.

The solution formulation has an alcohol base and will burn or irritate eyes, mucous membranes, and abraded skin. If the product gets into the eyes, mouth, or nose, these areas should be thoroughly rinsed with tap water. Patients should wash and dry the hands after using the product. These precautions also are intended to prevent the systemic entry of minoxidil by alternative routes. Products containing minoxidil should not be used on any other part of the body.²⁸

Product Selection Guidelines

Safety and efficacy of the product in children younger than 18 years have not been established, so the use of minoxidil in this age group is contraindicated.²²

The limited human and animal data available for topical minoxidil suggest moderate fetal risk.³⁷ Pregnant women should be advised to consult their primary care provider before using minoxidil. Minoxidil is excreted in breast milk. Even though the American Academy of Pediatrics considers minoxidil compatible with breastfeeding, patients should consult their primary care provider rather than merely initiating self-treatment with topical minoxidil.³⁷

Either the 2% solution or 5% foam formulations can be recommended for use

by women; however, men usually are advised to use the 5% concentration. One study demonstrated a lower incidence of contact dermatitis has been demonstrated with propylene glycol-free foam products than with topical solutions.^{1,21} Accordingly, the foam formulation *may* be more desirable in patients with a history of sensitive skin or dermatitis. Patient preference for method of application is a critical factor in product selection. **Table 45-4** lists examples of commercially available products.

TABLE 45-4 Selected Nonprescription Hair Regrowth Products	
Trade Name	Primary Ingredient
Hair Regrowth Treatment Men Topical Solution	Minoxidil 2%
Hair Regrowth Treatment Men Topical Solution	Minoxidil 5%
Minoxidil for Men 2% Topical Solution	Minoxidil 2%
Minoxidil for Men 5% Topical Solution	Minoxidil 5%
Men's Rogaine 5% Minoxidil Solution	Minoxidil 5%
Men's Rogaine 5% Minoxidil Unscented Foam	Minoxidil 5%
Women's Rogaine 5% Minoxidil Unscented Foam	Minoxidil 5%
Women's Rogaine 5% Minoxidil Solution	Minoxidil 2%
Theroxidil Topical Solution	Minoxidil 5%

Source: **References 22** and **28**; and Minoxidil (topical). Lexicomp Online, AHFS Essentials. Bethesda, MD: Wolters Kluwer Clinical Drug Information, Inc.; 2019. Available at: https://online-lexi-com.stlcpisa.stlcp.edu/lco/action/doc/retrieve/docid/essential_ashp/988087?cesid=8AywmY7UtA4&searchUrl=%2Fico%2Faction%2Fsearch%3Fq%3Drogaine%2520hair%2520regrowth%2520treatment%2520for%2520women%26t%3Dname%26va%3Drogaine#. Accessed November 27, 2019.

Complementary Therapies

In the past, FDA advisory panels have proposed removing from the market a number of ingredients that were known to be safe for external use but for

which scientific evidence was lacking for their purported efficacy in preventing hair loss or promoting hair growth.³⁸ These unsupported claims generally are no longer made, but many such ingredients are still available today in nonprescription lotions and shampoos. In addition, oral and topical dietary supplements marketed to improve the structure and function of hair growth have become more popular. Despite the lack of sufficient evidence to document effectiveness, shampoos, topical solutions, and dietary supplements for hair loss include ingredients such as amino acids, aminobenzoic acid, B vitamins, jojoba oil, lanolin, maidenhair fern (*Adiantum capillis-verneris*), polysorbates 20 and 60, royal jelly (white secretion of *Apis melliferis* worker bees), tetracaine hydrochloride, urea, and wheat germ oil.^{19,38,39} Saw palmetto administered orally was shown to increase hair growth in 6 of 10 men with AGA in one randomized, double-blind, placebo-controlled study.⁴⁰

Algorithm: Hair Loss

FIGURE 45–3 Self-care approach to management of hair loss. Key: D/C = Discontinue; PCP = primary care provider.

Assessment of Hair Loss: A Case-Based Approach

Before recommending a treatment for hair loss, the health care provider should first consider possible underlying medical causes. To assess for alopecia areata or telogen effluvium, the provider can direct the patient to perform a gentle hair-pull test. A positive result on this test is an indication for referral to a dermatologist or other appropriate specialist for further evaluation. If pathology-induced hair loss and active hair loss are ruled out, the assessment should determine whether the balding fits the criteria for AGA.

Cases 45–1 and 45–2 illustrate the assessment of patients with different forms of hair loss.

Case 45–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient seeks the pharmacist's advice regarding products to combat gradual hair loss at the temples with some thinning at the vertex; no signs of inflammation or scarring on scalp are evident.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	None
c. Description of the patient's efforts to relieve the symptoms	Patient has tried various "supplements" and switched shampoos several times, with no improvements noted.
d. Patient's identity	James Kramer
e. Patient's age, gender, height, and weight	30 years, male, 6 ft 2 in., 200 lb
f. Patient's occupation	Information technology support specialist
g. Patient's dietary habits	Hard-boiled eggs or oatmeal for breakfast; eats out for lunch daily, Mondays-Fridays; has fish or chicken with vegetables for dinner.
h. Patient's sleep habits	Sleeps 6-7 hours nightly.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Men's multivitamin daily; occasional ibuprofen 200-400 mg as needed for pain associated with past sports-related knee injury or headache
j. Allergies	Sulfa antibiotics (rash)
k. History of other adverse reactions to medications	None
l. Other (describe) _____	Mr. Kramer indicated that every male in his family eventually loses his hair. He prefers to use a topical

Relevant Evaluation Criteria	Scenario/Model Outcome
	treatment because he is concerned about adverse effects of oral medications.
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s) (Table 45-2).	The patient has androgenetic alopecia, as evidenced by typical male pattern hair loss: gradual hair loss at temples and vertex. He has no signs of inflammation or scarring on scalp. Eyebrows and eyelashes are normal.
3. Identify exclusions for self-treatment (Figure 45-3).	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Recommend self-care using nonprescription minoxidil topical treatment and/or camouflage measures. (2) Refer Mr. Kramer to his regular health care provider for evaluation and treatment. (3) Recommend self-care until an appropriate health care provider can be consulted. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Topical minoxidil 2% or 5% solution and 5% foam products are approved for use in men. Mr. Kramer can use either formulation along with nondrug measures to treat the alopecia. The 5% foam formulation may be preferred, as it may cause less irritation and be more effective.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Apply approximately ½ capful of 5% topical foam twice daily to a clean, dry scalp."
7. Explain to the patient or caregiver the rationale for selecting the recommended	"Minoxidil 2% or 5% solution and 5% foam are available and FDA approved for use in men with androgenetic alopecia. The foam formulation may cause less

Relevant Evaluation Criteria	Scenario/Model Outcome
therapeutic approach from the considered therapeutic alternatives.	irritation. Although either the 2% or 5% product will be effective, men using 5% minoxidil had an earlier response and greater hair regrowth than men using 2% minoxidil.”
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
a. Appropriate dose and frequency of administration	“Apply approximately ½ capful of 5% topical foam twice daily to a clean, dry scalp.”
b. Maximum number of days the therapy should be employed	“If no new hair growth is noted within 4–6 months, discuss continued use of the product with your primary care provider. If a response is noted, treatment will need to be continued indefinitely to maintain ongoing benefits.”
c. Product administration procedures	See Table 45–3 .
d. Expected time to onset of relief	“It may take 4–6 months for you to experience increased hair growth.”
e. Degree of relief that can be reasonably expected	“Progressive hair loss will be slowed.”
f. Most common adverse effects	“Local itching, irritation, and dryness or scaling at the site of application may occur.”
g. Adverse effects that warrant medical intervention should they occur	“Contact your primary care provider if you experience increased hair growth in areas beyond the scalp, acne, reddened skin/scalp, or swelling of the face.”
h. Patient options in the event that condition worsens or persists	“If increased hair growth is not experienced within 4–6 months, contact your primary care provider. Also contact your primary care provider if adverse effects are noted.”
i. Product storage requirements	“Store this product in a cool, dry place out of children’s

Relevant Evaluation Criteria	Scenario/Model Outcome
	reach.”
j. Specific nondrug measures	“Minimize exposure to factors that may trigger hair loss, such as certain medications, stress, illness, or injury.”
Solicit follow-up questions from the patient or caregiver.	“How can I tell if I am responding to the treatment?”
Answer the patient or caregiver questions.	“Hair density is more likely to increase if the treated area is in earlier stages of hair loss. Look for fine, short hairs as a first response. Additional hair loss may occur during the first few weeks of therapy.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Ask Mr. Kramer to call you right away with significant concerns about adverse effects (skin irritation, redness). Ask him to monitor and report any hair regrowth in 1–4 months.

Key: ACE = Angiotensin-converting enzyme; FDA = U.S. Food and Drug Administration; GERD = gastroesophageal reflux disease.

Case 45–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient’s symptoms and medical history, including	
a. Description of	The patient seeks the pharmacist’s advice regarding a

Relevant Evaluation Criteria	Scenario/Model Outcome
symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	significant increase in hair loss. She has noticed a large amount of shed hair in the shower drain and in the bathroom sink. The hair loss has resulted in noticeable diffuse thinning of the hair over the past several weeks. No signs of inflammation or scarring of the scalp are present. Hair-pull test gives a positive result (8 hairs are pulled from the scalp with gentle tugging on a group of approximately 50 hairs).
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	None
c. Description of the patient's efforts to relieve the symptoms	Patient has tried new vitamins to boost her energy and promote hair growth and switched shampoos without improvement.
d. Patient's identity	Jennifer Jones
e. Patient's age, gender, height, and weight	45 years, female, 5 ft 4 in., 180 lb
f. Patient's occupation	Graphic designer
g. Patient's dietary habits	Patient recently started a weight loss program at the local Y.
h. Patient's sleep habits	Sleeps about 10 hours a night.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Daily multivitamin; recently started taking fish oil for high cholesterol; Dulcolax occasionally for constipation
j. Allergies	None
k. History of other adverse reactions to medications	None
l. Other (describe) -----	The patient states: "I have been feeling extremely tired and down lately. I have gained quite a bit of weight over the past 2 months and have been more constipated. And now my hair is

Relevant Evaluation Criteria	Scenario/Model Outcome
	falling out! Even the men in my family generally keep their hair—I don't know what's going on with me!"
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s) (Table 45–2).	The patient likely has telogen effluvium secondary to hypothyroidism, as evidenced by relatively sudden onset of hair loss and a positive hair-pull test result. She also is extremely fatigued and has experienced weight gain and constipation. She has no signs of inflammation or scarring on the scalp.
3. Identify exclusions for self-treatment (Figure 45–3).	Hair loss of sudden onset with a positive result on a hair-pull test in a woman is suggestive of a possible endocrine disorder, so self-treatment is not an option.
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer Ms. Jones to her regular health care provider for evaluation and treatment. (2) Recommend self-care until she can see her primary care provider. (3) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Refer Ms. Jones to her regular health care provider for evaluation and treatment.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"You should consult your primary care provider for evaluation and treatment."
7. Explain to the patient or caregiver the rationale for selecting the	"The other signs and symptoms you described, such as weight gain and extreme fatigue, suggest that you may have an underlying cause for your hair loss, such as hypothyroidism. Use

Relevant Evaluation Criteria	Scenario/Model Outcome
recommended therapeutic approach from the considered therapeutic alternatives.	of nonprescription products available for hair loss is not recommended for this type of hair loss. It is best to see your primary care provider for evaluation and subsequent treatment.”
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
Solicit follow-up questions from the patient or caregiver.	“If the cause is identified and treated, will my hair grow back?”
Answer the patient’s or caregiver’s questions.	“If the underlying cause is identified and treated, hair loss will stop or lessen and hair will regrow. It is important to see your primary care provider to be evaluated and to determine appropriate treatment.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Ask Ms. Jones to report to you the outcome of her primary care provider’s evaluation and recommendations.

Patient Counseling for Hair Loss

Patients who want to use nonprescription minoxidil should be advised that most treatment regimens for hair loss do not alter its progression, and that the longer the hair thinning or loss has continued, the less likely it is that the agent will elicit a regrowth response. For patients who still want to use minoxidil, the health care provider should provide a careful review of product instructions, with emphasis on possible adverse effects and the signs and symptoms that

warrant medical attention. In addition, if hair regrowth is achieved, patient counseling should underscore the need for indefinite use of minoxidil to maintain the regrowth. Cosmetic products, camouflaging options, and hair transplants/surgical interventions may be acceptable alternatives if the patient is concerned about long-term use of the drug or does not obtain a desired endpoint with the minoxidil regimen. The box “Patient Education for Hair Loss” lists specific information to provide in patient counseling.

Evaluation of Patient Outcomes for Hair Loss

Patients should use minoxidil for the minimum recommended period. If new hair growth does not occur after use of minoxidil 2% or 5% for 4–6 months, the patient should consider ending treatment and consulting a dermatologist or other primary care provider for further evaluation.^{22,28} If new hair growth does occur within the recommended period, the patient should be advised to continue the drug treatment indefinitely.

Patient Education for Hair Loss

The goal in self-treatment for hair loss is to achieve an appearance that the patient considers acceptable while also minimizing emotional distress. This objective can be accomplished by nonprescription methods including cosmetic camouflage and/or the use of topical minoxidil to stimulate hair growth, when appropriate. To ensure optimal therapeutic outcomes, it is essential that patients carefully follow product packaging information and consider the following measures.

Nondrug Measures

- If desired, use wigs to cover severe hair loss until hair is regrown.
- For less severe hair loss, use hair sprays, gels, colorants, permanents, or hair-building products in moderation to create the illusion of full hair. These cosmetics will not affect the rate of hair loss.
- Avoid the use of oily hair products that can cause folliculitis.

- Avoid hairstyles that pull on the hair, such as tight braids.
- Avoid heat from hair dryers and curling/flat irons because their use can make the hair more brittle.

Nonprescription Medications

- During the first few weeks of minoxidil use, continued hair loss may occur. Note that use of minoxidil must be continuous and indefinite to maintain regrowth. Up to 4–6 months may be required to obtain any results. If treatment is interrupted, regrowth typically will be lost within 4 months or less, and progression of hair loss will begin again.
- Minoxidil is not recommended in patients who are pregnant, breastfeeding, or planning to become pregnant while using this product. Women should consult a primary care provider before initiating a minoxidil regimen.
- See Table 45–3 for instructions on how to use this product.
- Do not apply the product more often than directed. More frequent applications will not achieve better regrowth or a faster response but may increase adverse effects.
- Do not use other scalp drugs or hair care products while using this drug.
- Do not apply the product to damaged or inflamed areas of the scalp, including areas with active scalp psoriasis or eczema lesions and open scalp wounds of any kind.
- Note that local itching or irritation at the site of application may occur. More rarely, allergic contact dermatitis or transient hypertrichosis (unwanted facial hair growth) may occur.
- Keep product container in a cool, dry place, but do not put it in the refrigerator.
- Keep the product out of children's reach. Ingestion of minoxidil is potentially hazardous. If the product is ingested, a poison control center should be contacted immediately.
- The solution is flammable. Keep away from fire or flame.
- Do not use on infants or children 18 years of age or younger.
- Do not use if you have heart disease except under the supervision of a primary care provider.

- If hair fails to appear within the time specified on the product (generally 4–6 months) despite consistent use of the product, consider stopping the treatment and seeing your primary care provider for further evaluation.

Source: [References 22](#) and [28](#).

Key Points for Hair Loss

- Minoxidil is not effective for everyone.
- Positive treatment results may take several weeks to be noticed. Additional hair loss may occur during the first few weeks of therapy.
- Adherence is critically important for pharmacologic treatment. Hair loss will recur if therapy is stopped.
- Offering cosmetic solutions also may be helpful.
- Patients, particularly women, are seeking treatment not only to combat the hair loss but also to bolster self-esteem, which often suffers because of the cultural association of hair loss with illness and advanced age.
- The health care provider should identify and acknowledge the limitations of the ongoing treatment and provide emotional support.

Chapter 46: Insomnia, Drowsiness, and Fatigue

Authors: Christine Eisenhower

Insomnia

Insomnia, one of the most common patient complaints, is associated with increasing age, female sex, several comorbid disorders, and night shift work.¹ Insomnia occurs when a person has trouble falling or staying asleep and/or does not feel refreshed after sleeping, despite having the opportunity to sleep for an adequate amount of time in a sufficient environment.^{1,2} Insomnia results in poor daytime productivity, impaired functional status, work absenteeism, and occupational and motor vehicle accidents.¹ Annual cost estimates for insomnia in the United States range from \$30 billion to \$107.5 billion, depending on inclusion of indirect costs such as missed workdays.³

The National Sleep Foundation recommends 7–9 hours of sleep nightly for adults ages 26–64 years, and 7–8 hours for adults 65 years and older.^{4,5} The typical American gets 6.9 hours of sleep on workdays and 7.6 hours on non-workdays.⁵ In a 2015 poll, 34% of Americans reported at least one sleep problem during the previous 7 days, and 13% reported they rarely or never get a good night of sleep.⁵ Weekly average sleep duration is lowest for those who rate their general health, quality of life, and/or physical and mental health as fair or poor.⁵ Approximately 20% of American adults use a medication for insomnia in a given month, with nearly 60% of medications used being nonprescription sleep aids, primarily antihistamines.⁶ Only a small percentage of patients with symptoms of insomnia actually consult their health care provider.⁶ The combination of frequent misuse of hypnotics and availability of nonprescription agents makes insomnia a disorder of significant concern.

Pathophysiology of Insomnia

Sleep comprises five different stages. Stages 1–4, categorized as non-rapid eye movement (REM) sleep, are important for overall health maintenance. Stage 5 is important for regulation of learning and mood.^{3,7} *Stage 1 sleep* is a transitional stage, representing the initiation of sleep.⁷ *Stage 2* is an

intermediate phase involving alpha rapid-wave sleep, as measured by an electroencephalogram (EEG). At this stage, heart rate and body temperature decrease.^{3,7} Stages 3 and 4, collectively known as *deep sleep* or *delta sleep*, are characterized by the patterns of delta or slow-frequency waves on the EEG. Stage 5, or *REM sleep*, is neither light nor deep and is characterized by an increase in dream activity. At this stage, the EEG demonstrates an increase in high-frequency waves.⁷ The whole sleep cycle takes place over 90–120 minutes, with about 3–7 cycles occurring per night.³

Sleep physiology changes with increasing age. Among older adults, total sleep time is shorter, the number of nocturnal awakenings increases, and less time is spent in stages 4 and 5. *Sleep-onset latency* (time to fall asleep) usually remains normal with increasing age. Despite these changes, older adults cannot be assumed to require less sleep.⁵

Shift workers often complain of sleep disturbances and fatigue. Night shift work can have negative impacts on the circadian rhythm and secretion of melatonin, stress hormone levels, autoimmune function, work–life balance, social interactions, and mental health. Those who work rotating night shifts with early shift changeovers and backward-rotating shifts may have an even higher risk of health problems.⁸

Insomnia can be classified on the basis of an identifiable cause. *Primary insomnia* is the term used to describe patients who have sleep difficulty that may be considered idiopathic, paradoxical, or psychophysiological.² *Paradoxical insomnia* is defined as the presence of significant sleep symptoms with poor correlation between patient report of symptoms and objective measures of sleep.^{2,6} Patients also may have primary insomnia caused by inadequate sleep hygiene or acute stressors such as medical illness, anxiety, travel, hospitalization, divorce, or death of a loved one (known as *adjustment insomnia*).¹ *Secondary insomnia* is caused by another sleep disorder, general medical or psychiatric condition, substance use disorder, or medication(s).² All underlying causes of insomnia should be identified and, if possible, managed to relieve the sleep disturbance.^{2,3}

Insomnia also can be classified as *short-term* or *chronic* according to the duration of sleep disturbance. Short-term insomnia meets the symptom criteria and persists <3 months.¹ Chronic insomnia persists ≥3 months with symptoms occurring ≥3 times per week; it can be secondary to medical problems, psychiatric disorders, or a substance use disorder.¹ Short-term

insomnia affects an estimated 30%–50% of the population, whereas chronic insomnia affects at least 5%–10% of the population in industrialized countries.¹

In addition to psychiatric disorders, several medical disorders are associated with chronic insomnia ([Table 46–1](#)). Chronic insomnia is a key complaint of patients experiencing pain syndromes. It also can be secondary to use of medications or other substances, or to *circadian rhythm sleep disorders*; the latter involves abnormalities in length, timing, and/or rigid behavior of the sleep–wake cycle relative to the day–night cycle.^{2,6} Early morning awakening often is associated with depression. Nonprescription sleep aids generally are not helpful in patients with chronic insomnia, and medical referral is indicated.

TABLE 46–1 Medical Disorders Associated With Insomnia

General Medical Disorders
Allergies
Arthritis
Benign prostatic hyperplasia
Chronic pain syndromes
Diabetes mellitus
Gastroesophageal reflux disease
Heart failure
Incontinence
Irritable bowel syndrome
Peptic ulcer disease
Respiratory Disorders
Asthma
Chronic obstructive pulmonary disease
Psychiatric Disorders
Anxiety disorders

Depression
Substance use disorders
Sleep Disorders
Obstructive sleep apnea
Psychophysiologic insomnia
Restless legs syndrome
Shift-work sleep disorder
Other Conditions
Menopause
Pregnancy

Source: [References 2](#) and [3](#).

Medications, including both prescription and nonprescription drugs, can produce either insomnia or withdrawal insomnia ([Table 46–2](#)).^{2,7,9,10} Antidepressants, antihypertensive agents, and sympathomimetic amines such as pseudoephedrine and phenylephrine are commonly associated with insomnia. Alcohol can cause insomnia after acute use and as a withdrawal effect after chronic use. Some individuals also are sensitive to the stimulant effects of caffeine and nicotine. Drinking caffeinated beverages in the late afternoon or evening hours can cause insomnia. Late-night exercise, late-evening meals, and environmental distractions such as noise, lighting, uncomfortable temperatures, or new surroundings also can interfere with sleep.⁷

TABLE 46–2 Selected Drugs That Can Exacerbate Insomnia

Drugs That Can Cause Insomnia	Drugs That Can Produce Withdrawal Insomnia
Alcohol	Alcohol
Antiarrhythmics	Amphetamines
Antidepressants (e.g., bupropion, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors)	Antihistamines (first generation) Barbiturates Benzodiazepines Illicit drugs (e.g., cocaine, marijuana, phencyclidine)
Antihypertensives (e.g., beta-blockers, diuretics, alpha-receptor agonists and antagonists)	Monoamine oxidase inhibitors
Amphetamines	Opiates
Beta-adrenergic agonists (e.g., albuterol)	Tricyclic antidepressants
Caffeine	
Corticosteroids	
Decongestants	
Diuretics (at bedtime)	
Nicotine	
Theophylline	
Thyroid preparations	

Source: [References 2, 7, 9, and 10](#).

Clinical Presentation of Insomnia

Patients with insomnia may have varying complaints, such as difficulty falling

asleep, frequent awakenings, early morning awakening and inability to fall back to sleep, disturbed quality of sleep with unusual or troublesome dreams, or just poor sleep quality. Their actual duration of sleep, as determined by sleep laboratory studies, may or may not differ from individuals who report normal sleep. However, these patients may report that they need more than 30 minutes to fall asleep and/or that their duration of sleep is less than 7 hours nightly.

Sleep-deprived individuals are highly symptomatic, and their quality of life is negatively affected. Most untreated patients with insomnia report symptoms of fatigue, drowsiness, anxiety, irritability, depression, decreased concentration, and memory impairment. If untreated, insomnia can be associated with a rise in morbidity and mortality rates from general medical and psychiatric disorders, such as cardiovascular disease, pain syndromes, depression, anxiety, and substance use disorder.^{2,6}

Treatment of Insomnia

Treatment Goals

Treatment goals are to improve the patient's presenting symptoms, quality of life, and functioning.² This may be achieved through modification of concomitant medications, management of related medical conditions, and use of nonpharmacologic and pharmacologic therapies for insomnia.

General Treatment Approach

For patients with transient or short-term primary insomnia, reestablishing the normal sleep cycle with good sleep hygiene practices, with or without a nonprescription sleep aid, should help to normalize sleep patterns. Patients with an average sleep-onset latency greater than 30 minutes, wake after sleep onset (WASO) greater than 30 minutes, sleep efficiency less than 85%, and/or total sleep time less than 6.5 hours are described in the literature as having significant sleep disturbances and should be referred to their health care provider. *Sleep efficiency* describes the percent of time in bed that the patient is actually asleep.^{2,7} Patients with other sleep disorders, such as sleep apnea, narcolepsy, and restless legs syndrome, also may seek relief with the use of nonprescription sleep aids. Because of the risk for potentially significant adverse effects, patients with these disorders require medical referral to a

sleep specialist. The algorithm in [Figure 46–1](#) outlines the assessment and self-treatment of transient and short-term insomnia, and also lists exclusions for self-treatment.

Nonpharmacologic Therapy

Cognitive behavioral therapy for insomnia (CBT-I), which addresses dysfunctional behaviors and beliefs that contribute to insomnia, is considered first-line therapy for all patients.^{1,6,11} CBT-I consists of a combination of cognitive therapy; behavioral interventions such as sleep restriction, relaxation, and stimulus control; and educational interventions such as sleep hygiene.¹² *Sleep restriction* is a method of reducing daytime sleepiness and improving sleep continuity that entails limiting time in bed (TIB) to just sleeping at night. Patients should be asked to record how much time they actually were asleep (total sleep time). Initially, TIB is limited to that total sleep time (no daytime napping) and then gradually increased to enhance sleep drive. For example, a patient may spend 9 hours in bed but sleep only 6.5 hours. The patient should restrict TIB to 6.5 hours and avoid daytime napping. Initially, the patient will experience daytime sleepiness, but the patient's body will adjust and the sleep drive will increase in about 1 week. The patient can then extend TIB by an additional 30 minutes each week; eventually, the total sleep time will be confined only to nighttime. This approach also will reduce nighttime awakenings.²

The use of weekly CBT-I in both group therapy at a mentalhealth care center and guided internet therapy with a sleep therapist has been evaluated in adolescents with insomnia, with improvements observed in sleep efficiency, sleep-onset latency, WASO time, and total sleep time.¹² The sleep hygiene measures in [Table 46–3](#) are recommended for all patients with insomnia.^{6,7,11,13} In most patients with sleep disturbances, these measures should be tried before starting drug therapy. If initiated, drug therapy should be accompanied by sleep hygiene and other components of CBT-I.¹ Patients should be encouraged to try one or two measures at a time. Barriers to implementation of CBT-I include cost, and patients' lack of availability or patience, and/or unwillingness to try CBT-I techniques.¹

TABLE 46–3 Principles of Good Sleep Hygiene

- Use bed for sleeping or intimacy only.
- Establish a regular sleep pattern. Go to bed and arise at about the same time daily, even on the weekends.
- Make the bedroom comfortable for sleeping. Avoid temperature extremes, noise, and light.
- Engage in relaxing activities before bedtime.
- Avoid using electronic devices (particularly television and smart devices) around bedtime.
- Exercise regularly but not within a few hours of bedtime.
- If hungry eat a light snack but avoid eating meals within 2 hours before bedtime.
- Avoid daytime napping or limit naps to 20–30 minutes.
- Avoid using caffeine, alcohol, or nicotine for at least several hours before bedtime.
- If unable to fall asleep after more than 20 minutes, do not continue to try to sleep; get out of bed and perform a relaxing activity until you feel tired.
- Do not watch the clock at night.

Source: [References 6, 7, 11, and 13](#).

Pharmacologic Therapy

When the U.S. Food and Drug Administration (FDA) issued its final monograph on nonprescription sleep aids in 1989, the antihistamine diphenhydramine, as either the hydrochloride or citrate salt, was the only sleep aid deemed to be safe and effective for self-administration.¹⁴

Antihistamines

Diphenhydramine and doxylamine belong to the ethanolamine group of antihistamines, which affect sleep by competitively blocking histamine-1 receptors.^{15,16} Although the safety and efficacy of doxylamine have not been fully established, FDA has allowed the drug to remain on the market. Few studies supporting the efficacy of doxylamine as a hypnotic are available.^{17,18}

Both diphenhydramine and doxylamine are well absorbed from the gastrointestinal tract, with similar times to maximum plasma concentrations (1–4 hours and 2–4 hours, respectively). Diphenhydramine has an elimination half-life of 2.4–9.3 hours in healthy adults compared with 10–12 hours for doxylamine.^{15,17} Diphenhydramine is metabolized in the liver through two successive N-demethylations, and its apparent half-life can be prolonged in

patients with hepatic cirrhosis.¹⁵ Studies have shown a positive relationship between diphenhydramine plasma concentrations and drowsiness and cognitive impairment. Maximum sedation with diphenhydramine occurs 1–3 hours after a dose.¹⁵

The primary indication for diphenhydramine in insomnia is the symptomatic management of transient and short-term sleep difficulties, particularly in individuals who complain of occasional problems falling asleep. The efficacy of diphenhydramine in patients with chronic insomnia is poor.¹⁸ Tolerance to the sedative effect of diphenhydramine develops in healthy volunteers within days of repeated use.¹⁸

For use as a nighttime sleep aid, the usual diphenhydramine dosage is 50 mg for patients 12 years and older, taken 30 minutes prior to bedtime. Use of a 100 mg dose is not likely to be more efficacious but will increase the risk for adverse effects.¹⁵ Intermittent use to assess sleep quality without medication may reduce tolerance to the hypnotic effect. Use of diphenhydramine as a sleep aid should be limited according to the 2017 American Academy of Sleep Medicine (AASM) guidelines.¹

Additive sedation or anticholinergic effects occur when diphenhydramine is taken with other medications having these properties.¹⁹ For example, diphenhydramine, an inhibitor of the hepatic enzyme cytochrome P450 2D6 (CYP2D6), causes more than a twofold decrease in the clearance of metoprolol, especially in women.²⁰ Table 46–4 describes clinically significant drug–drug interactions that can occur with diphenhydramine.^{16,20,21} Alterations to pharmacotherapy should be made, if indicated.

TABLE 46–4 Selected Clinically Significant Drug Interactions With Diphenhydramine

Interacting Drugs or Drug Classes	Description	Monitoring Recommendation
Acetylcholinesterase inhibitors	Acetylcholinesterase inhibitors and diphenhydramine may diminish the therapeutic effects of each other.	Monitor therapy.
Alcohol (ethyl)	Diphenhydramine may enhance the central nervous system (CNS)	Monitor therapy.

Interacting Drugs or Drug Classes	Description	Monitoring Recommendation
	depressant effect of ethanol.	
Aripiprazole	Diphenhydramine may increase serum concentrations of aripiprazole.	Monitor for increased pharmacologic effects. Dose adjustments may be required based on concomitant therapy and/or indication.
Buprenorphine	Diphenhydramine may enhance the CNS depressant effect of buprenorphine.	Consider reduced doses of other CNS depressants, and avoiding such drugs in patients at high risk of buprenorphine overuse/self-injection. Initiate buprenorphine patches at 5 mcg per hour when used with other CNS depressants.
Cannabinoids	Cannabinoids may enhance the CNS depressant effect of diphenhydramine.	Monitor therapy.
Gastrointestinal Agents (prokinetic)	Diphenhydramine may diminish the therapeutic effect of prokinetic gastrointestinal (GI) agents.	Monitor therapy.
Glucagon	Diphenhydramine may enhance the adverse and toxic GI effects of glucagon.	Monitor therapy.
Kava	Kava may enhance the adverse/toxic effects of diphenhydramine.	Monitor therapy.
Magnesium sulfate	Magnesium sulfate may enhance the CNS depressant effect of diphenhydramine.	Monitor therapy.
Metoprolol	Diphenhydramine may increase the serum concentration of metoprolol and cause negative chronotropic	Consider an alternative for one of the interacting drugs to avoid metoprolol toxicity. If the combination must be used, closely monitor response to metoprolol. Metoprolol dose reductions may be

Interacting Drugs or Drug Classes	Description	Monitoring Recommendation
	effects, particularly in women.	necessary.
Minocycline	Minocycline may enhance the CNS depressant effect of diphenhydramine.	Monitor therapy.
Mirtazapine	Diphenhydramine may enhance the CNS depressant effect of mirtazapine.	Monitor therapy.
Opioid agonists	Diphenhydramine may enhance the CNS depressant effect of opioid agonists.	Avoid concomitant use; only combine if alternatives are ineffective or unavailable.
Potassium chloride	Diphenhydramine may enhance the ulcerogenic effect of potassium chloride.	Patients on diphenhydramine should avoid using any solid oral dosage form of potassium chloride because of anticholinergic effects. Avoid combining use of these drugs.
QT-prolonging agents (e.g. antiarrhythmics, citalopram, clarithromycin, fluoxetine, levofloxacin, moxifloxacin, ziprasidone)	Additive QT-prolonging effects occur with diphenhydramine.	Unless contraindicated, coadminister with caution.
Selective serotonin reuptake inhibitors (SSRIs)	Diphenhydramine may enhance the adverse effects of SSRIs. Risk of psychomotor impairment may be enhanced.	Monitor therapy.
Tamoxifen	Histamine-1 receptor blockers may decrease serum concentrations of endoxifen, the active metabolite of tamoxifen.	When possible, consider alternatives that have less of an inhibitory effect on CYP2D6 activity. Consider therapy modification.

Interacting Drugs or Drug Classes	Description	Monitoring Recommendation
Topiramate	Diphenhydramine may enhance the adverse and toxic effects of topiramate.	Monitor therapy.

Source: [References 16, 20, and 21](#).

The primary adverse effects of diphenhydramine and doxylamine are anticholinergic.^{15,17} Dry mouth and throat, constipation, blurred vision, urinary retention, and tinnitus may occur. Older patients, patients with comorbid medical disorders, and patients taking multiple medications are particularly susceptible to developing adverse effects when taking either sleep aid.

Anticholinergic toxicity can result from excessive antihistamine dosages. Factors such as drug–drug interactions, intentional overdose, or individual sensitivity also can lead to toxicity.^{16,19} Central nervous system (CNS) anticholinergic toxicity is one of the primary presenting features of antihistamine excess. Patients exhibiting excessive anticholinergic effects can be anxious, excited, delirious, hallucinating, or stuporous. In more-severe cases, coma or seizures may occur. Other physical signs of anticholinergic toxicity include dilated pupils, flushed skin, hot and dry mucous membranes, and elevated body temperature. Tachycardia and moderate QTc prolongation on the electrocardiogram are common. In severe cases, rhabdomyolysis, dysrhythmias, cardiovascular collapse, hallucinations, seizure, and death can occur.^{16,19} In the case of diphenhydramine overdose, patients should be referred for emergency treatment, which includes gastric lavage and activated charcoal administered orally or via nasogastric tube, and additional symptomatic treatment.¹⁶

Several warnings and precautions apply to the use of diphenhydramine. Older men with prostatic hyperplasia and difficulty urinating should not use diphenhydramine because urinary retention can occur. Anticholinergic agents can increase intraocular pressure; therefore, patients with angle-closure glaucoma should avoid them. Patients with hypertension or ischemic heart

disease are advised to use diphenhydramine with caution. However, cardiovascular adverse effects such as hypotension and arrhythmias are not common and are generally associated with overdoses.^{16,19} Anticholinergic agents decrease cognitive function and increase confusion in patients with dementia; these patients should not take diphenhydramine because it is categorized as having definite anticholinergic effects on the Anticholinergic Cognitive Burden Scale.²² In addition, higher cumulative anticholinergic use is associated with an increased risk for dementia. Efforts to increase awareness among health care providers and older adults about this potential medication-related risk are important to minimize use of anticholinergic medications such as diphenhydramine over time.²³

Patients should be cautioned to avoid performing tasks that require their full attention or coordination, such as driving, cooking, or operating machinery, until their response to diphenhydramine is known. They also should be discouraged from drinking alcoholic beverages while taking diphenhydramine. Some patients can develop excitation from diphenhydramine and other highly anticholinergic antihistamines.¹⁹ This paradoxical effect occurs more often in children, older patients, and patients with organic mental disorders. Symptoms include nervousness, restlessness, agitation, tremors, insomnia, delirium, and, in rare cases, seizures.

Combination products containing diphenhydramine plus acetaminophen, ibuprofen, or aspirin are available.^{16,19} No published studies establish whether these products are of benefit in inducing sleep in patients who complain of insomnia caused by pain. Gastrointestinal adverse effects are of concern with frequent use of combination products containing ibuprofen and aspirin.

Several case reports of diphenhydramine use disorder in patients taking antipsychotic medications have been published.²⁴ Health care providers should carefully assess for misuse in individuals making repeated purchases of diphenhydramine, especially in patients being treated for psychosis. Patients taking antipsychotics may seek relief of adverse effects, such as tremor, and rewarding effects, such as elevated mood from anticholinergic medications.²⁴

Ethanol

Use of alcohol as a hypnotic is common in patients with chronic insomnia who wish to shorten time to sleep onset. However, alcohol has a short duration of action and is associated with adverse effects such as misuse, dependence, and

exacerbation of obstructive sleep apnea.² The Intraindividual Study of Affect, Health, and Interpersonal Behavior (iSAHIB) evaluated sleep quality and alcohol consumption in 150 participants 19–89 years of age. Results showed significant and negative associations between sleep quality and daily alcohol use. Use of items from the Pittsburgh Sleep Quality Index showed a decrease of 0.71 in sleep quality for each additional drink.²⁵

Alcohol is present in some liquid nonprescription combination cold products. These products can contain up to 10% alcohol by volume and are marketed to induce sleep. However, data regarding the efficacy and safety of these products as sleep aids are limited. The multiple ingredients increase the risk of adverse effects and interactions with other drugs.

Pharmacotherapeutic Comparisons

In general, diphenhydramine should not be recommended for a chronic sleep disturbance because use-related adverse effects are common, especially in older adults, and evidence of efficacy is lacking.^{2,6,11,18} AASM’s weak recommendation against the use of diphenhydramine for treatment of sleep-onset and sleep-maintenance insomnia is based on low-quality evidence in patients receiving 50 mg doses.¹

Product Selection Guidelines

Because the value of doxylamine as a sleep aid is not well established, only diphenhydramine may be suggested to appropriate patients for short-term use. To meet different patient preferences, nonprescription diphenhydramine is available as capsules, liquid-filled capsules, caplets, tablets, chewable tablets, orally disintegrating tablets, solutions, and elixirs (Table 46–5).¹⁶

TABLE 46–5 Selected Nonprescription Sleep Aid Products	
Trade Name	Primary Ingredient(s)
Single-Entity Antihistamine Products	
Unisom SleepGels Capsules (liquid filled)	Diphenhydramine HCl 50 mg
Unisom SleepMelts Tablets (orally disintegrating)	Diphenhydramine HCl 25 mg
Sominex Nighttime Sleep-Aid Tablets	Diphenhydramine HCl 25 mg

Trade Name	Primary Ingredient(s)
Sominex Nighttime Sleep-Aid Caplets	Diphenhydramine HCl 50 mg
ZzzQuil Nighttime Sleep-Aid Capsules (liquid filled)	Diphenhydramine HCl 25 mg
ZzzQuil Nighttime Sleep-Aid Liquid	Diphenhydramine HCL 50 mg/30 mL
Antihistamine/Analgesic Combination Products	
Advil PM Pain Reliever & Nighttime Sleep Aid Caplets	Diphenhydramine citrate 38 mg; ibuprofen 200 mg
Excedrin PM Headache Caplets	Diphenhydramine citrate 38 mg; acetaminophen 250 mg; aspirin 250 mg
Tylenol PM Extra Strength Caplets	Diphenhydramine HCl 25 mg; acetaminophen 500 mg
Tylenol PM Extra Strength Pain Reliever and Sleep Aid Liquid	Diphenhydramine HCl 50 mg; acetaminophen 1000 mg; per 30 mL

Note: Information is not all-inclusive. Product formulations may have changed since time of publication.

Special Populations

The safety of antihistamines during pregnancy has not been established.¹⁹ Therefore, the benefit–risk ratio of using these drugs to manage insomnia during pregnancy should be evaluated carefully. Most epidemiologic studies have not demonstrated increased risk of teratogenicity with the use of diphenhydramine during the first trimester, but one trial from 1974 reported cleft palate alone and other fetal abnormalities.¹⁵ Nevertheless, pregnant women should be referred for further evaluation.

An increased risk of CNS adverse effects can occur in breastfed neonates after maternal intake of a sedating antihistamine. Use of large dosages for sustained periods of time may inhibit lactation, causing drowsiness and irritability in breastfed infants.^{16,26} Continued use of sedating antihistamines for insomnia is not recommended for use in nursing mothers.^{16,17,19} Second-generation antihistamines are preferred for women who are breastfeeding and require

use of an antihistamine.¹⁶

Children and adolescents may present with insomnia caused by a circadian rhythm disorder. Teenagers should be asked about their use of nonprescription remedies and intake of caffeine, nicotine, alcohol, and illicit substances. Behavioral interventions and good sleep hygiene are first-line treatment for insomnia in children and adolescents. Diphenhydramine and doxylamine are not indicated to treat insomnia in children younger than 12 years. Diphenhydramine may cause paradoxical excitation in younger children and is not recommended to induce sleep in infants.¹⁵ Anticholinergic toxicity is common in children, and their symptoms may be more severe than those of adults. Diphenhydramine toxicity was reported in children administered the topical application over large areas of their bodies, as well as in those receiving topical and oral preparations simultaneously.¹⁵ FDA requires a label warning that advises consumers not to use oral nonprescription diphenhydramine with other products that contain the drug, including topical agents.¹⁵

Treatment of insomnia in older adults involves behavioral therapy and pharmacotherapy with approved agents. The 2019 AGS Beers Criteria[®] recommends avoiding the use of first-generation antihistamines in older adults (age $\geq$ 65 years) because of their anticholinergic effects.²⁷ Concerns about diphenhydramine and doxylamine use in older patients include delirium, confusion, and cognitive decline. Therefore, nonprescription antihistamines should not be recommended to treat insomnia in this age group; the patients should be referred instead to their health care provider for further evaluation.

Patient Factors

Considerations for selecting nonprescription and/or complementary therapies for insomnia include the patient's age, their participation in shift-work, and their willingness to make changes to their sleep hygiene and routine. Product cost and availability are other considerations.

Patient Preferences

Patients may prefer the use of diphenhydramine as a more effortless intervention over CBT-I measures. However, they should be reminded of the potential benefits of CBT-I, and the lack of evidence to support use of diphenhydramine and other nonprescription therapies for insomnia.

Complementary Therapies

Complementary therapies such as melatonin, valerian, and chamomile often are used for insomnia. (See [Chapter 51](#) for a thorough discussion of these first two supplements). The AASM's weak recommendation against the use of melatonin or valerian as treatment for sleep-onset or sleep-maintenance insomnia in adults is based on evidence of very low and low quality, respectively.¹ The recommendation against melatonin is based on the use of 2 mg doses, which reduced sleep-onset latency by an average of 9 minutes versus placebo, but demonstrated only small improvements in sleep quality.¹ However, a systematic review of six placebo-controlled trials concluded that both melatonin immediate-release 5 mg daily for 8 weeks and extended-release 2 mg daily for 3 weeks benefited patient-reported sleep quality, sleep-onset latency, and morning alertness. Patients receiving 2 mg doses continued to see positive effects on sleep-onset latency at 26 weeks.¹⁸ Overall, evidence of the efficacy of melatonin is conflicting and likely depends on many factors such as dosing and timing of administration. Melatonin may be given 2–3 hours prior to bedtime to shift circadian rhythm. With regard to safety, a small study of patients aged ≥55 years did not observe psychomotor or cognitive impairment with use of melatonin.¹⁸ Patients who choose to try melatonin using the aforementioned doses and formulations should be advised to contact their health care provider after 10 days if insomnia persists.

Compared with placebo, valerian (*Valeriana officinalis*) lacks benefit in insomnia.²⁸ A meta-analysis of five randomized, double-blind, controlled trials reported no statistically significant differences in sleep-onset latency, sleep duration, sleep efficiency, and wake duration.²⁸ Various doses of valerian concoctions and extracts were used in clinical trials, including 300–600 mg daily taken 30–60 minute prior to bedtime, and 100–1215 mg 3 times daily.²⁸ A higher incidence of adverse events, including diarrhea, was observed in eight trials comparing valerian with placebo.²⁸

Chamomile (*Matricaria recutita*) flower extract is considered a popular dietary supplement to induce drowsiness.^{28,29} Chamomile contains apigenin, a flavonoid that antagonizes GABA-A and GABA-C receptors.²⁹ A small study of adults with primary insomnia compared use of a placebo with 270 mg of flower extract (higher than the dose ingested in tea) twice daily for 4 weeks.^{28,29} Statistically significant differences in severity were not detected for insomnia, sleep-onset latency, WASO time, sleep duration, nocturnal

awakenings, daytime functioning, sleep quality, and sleep efficiency.²⁸

Mindfulness meditation may be a useful complementary therapy for patients with insomnia. It involves attention regulation, body awareness, emotional regulation, and self-awareness. A meta-analysis of six randomized, controlled trials that included patients with primary chronic insomnia, insomnia secondary to depression or cancer, and sleep disturbances reported significant improvements in total wake time ($P = .03$) and sleep quality ($P = .003$).³⁰

Assessment of Insomnia: A Case-Based Approach

In assessing whether to recommend a nonprescription sleep aid, the health care provider should determine whether use of such products is appropriate, what nondrug interventions should be recommended, and whether medical referral to another provider is indicated. Identifying acute causes of insomnia, poor sleep hygiene practices, or underlying medical disorders can assist the provider in making a recommendation.

Case 46–1 is an example of the assessment of a patient with insomnia.

Algorithm: Transient and Short-Term Insomnia

FIGURE 46–1 Self-care of transient and short-term insomnia. Key: CBT-I = Cognitive behavioral therapy for insomnia; WASO = wake after sleep onset.

Case 46–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	

Relevant Evaluation Criteria	Scenario/Model Outcome
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient complains of difficulty sleeping for the past 2 months. He lies awake about 20 minutes before going to sleep and is often drowsy and irritable at work. He wakes up 2–3 times per night, for about 5 minutes each time.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Patient reports he previously slept well, except when stressed at work. His work schedule recently changed; he works 4 days per week from 6 AM to 2 PM and covers a nighttime shift on Saturdays as an air traffic controller. His sleep difficulties began after this change.
c. Description of the patient's/ caregiver's efforts to relieve the symptoms	He reports playing games on his smart phone if he cannot fall asleep right away. He lives with his spouse and two young children, so he finds the weekend shift to be the most challenging to his sleep routine. Sometimes, he sleeps in the basement to avoid extra noise. If he cannot get enough sleep, he will drink two cups of coffee before the next shift starts.
d. Patient's identity	Dan Rudy
e. Patient's age, gender, height, and weight	43 years old, male, 5 ft 9 in., 182 lb
f. Patient's occupation	Air traffic controller for Federal Aviation Administration
g. Patient's dietary habits	Patient reports stopping at the local coffee shop for one donut, one bagel, and two coffees most mornings. His spouse packs a lunch for him on the weekdays, usually consisting of a turkey sandwich and sometimes a leftover salad. He also will grab a large candy bar from the

Relevant Evaluation Criteria	Scenario/Model Outcome
	vending machine each afternoon and another coffee halfway through his shift. He also drinks two more coffees in the evening if he needs to be awake to drive his kids to soccer and dance.
h. Patient's sleep habits	Can get about 8 hours of sleep after weekday shifts but decreases to just under 7 hours after nighttime shift for a few days.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	<i>High cholesterol:</i> Atorvastatin 20 mg daily; <i>pain from old knee injury:</i> ibuprofen 800 mg as needed
j. Allergies	No known drug allergies
k. History of other adverse reactions to medications	None
l. Other (describe) _____	Drinks "a few" beers with his friends on Friday nights or when watching football games. Denies use of tobacco.
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Poor sleep secondary to shift-work, which occurs in a semi-dark room. Excessive caffeine use late in day. Poor sleep hygiene due to use of smart device when he cannot fall asleep.
3. Identify exclusions for self-treatment (Figure 46-1).	None
4. Formulate a comprehensive list of therapeutic alternatives for the	Options include (1) Refer Dan to his HCP.

Relevant Evaluation Criteria	Scenario/Model Outcome
primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	(2) Recommend CBT-I techniques until Dan can make an appointment with his HCP. (3) Recommend diphenhydramine 50 mg after Saturday shift, and CBT-I measures including good sleep hygiene after all shifts, limiting daily alcohol and caffeine use, and engaging in regular physical activity. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	CBT-I measures including good sleep hygiene for 10 days, as well as limiting alcohol and caffeine consumption. May try diphenhydramine after nighttime shift.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Take 1 diphenhydramine 50 mg tablet 30 minutes before your anticipated bedtime after your Saturday shift. If symptoms persist for 10 days, seek medical evaluation."
	"Follow measures for positive sleep hygiene." (See Table 46-3.) "Limit alcohol consumption to 1-2 servings (12-24 oz) of beer, consumed no later than 2 hours before bedtime. Limit overall intake of caffeine, and at a minimum, avoid caffeine 6 hours before bedtime."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the	"A consistent sleep pattern will help resolve your insomnia. Seeing your health care provider may not be necessary if you follow good sleep hygiene measures and take the diphenhydramine. Poor sleep practices are a common cause of insomnia. If these practices are continued, they can create a chronic sleep disturbance. A medication such as diphenhydramine can facilitate falling asleep, but it must be combined with measures of good sleep hygiene. You should avoid screen time

Relevant Evaluation Criteria	Scenario/Model Outcome
considered therapeutic alternatives.	from your cell phone at night because the bright light can interfere with your ability to fall asleep. In addition, you may find mindfulness mediation as well as sleep restriction to be helpful.”
	“Alcohol in more than modest quantities can disrupt sleep and make insomnia worse. Therefore, alcohol consumption should be limited and avoided for at least 2 hours before bedtime. In addition, caffeine is a stimulant and promotes wakefulness. Caffeine intake should be limited and not occur within 6 hours of bedtime. All dietary sources of caffeine, for example, coffee, sodas, and energy drinks, as well as hidden sources of caffeine, such as chocolate, should be identified.”
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	“Take diphenhydramine 50 mg nightly after your Saturday shift. Do not exceed this nightly dose. Always use sleep aids in combination with good sleep hygiene measures.” (See Table 46–3). “Do not take diphenhydramine as a sleep aid for more than a few nights without seeing your health care provider.”
	“Avoid drinking alcohol with the diphenhydramine because of the risk of increased sedation and the negative effects that alcohol has on sleep patterns.”
	“Adverse effects may include sedation, next-morning hangover, and anticholinergic effects such as dry mouth, urinary retention, blurry vision, and constipation.”
Solicit follow-up questions from the patient or caregiver.	(1) “May I repeat the dose of diphenhydramine if I do not fall asleep within 2 hours?” (2) “May I take diphenhydramine with my cholesterol medication?”
Answer the patient’s or caregiver’s	(1) “No. Repeating the dose increases the risk of side effects and likely will not improve sleep.” (2) “You may take both medications at the same time because

Relevant Evaluation Criteria	Scenario/Model Outcome
questions.	diphenhydramine has no significant interaction with your cholesterol medication.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact the patient after at least 3 days and one Saturday shift to assess the efficacy of diphenhydramine and improved sleep hygiene measures. Remind the patient if the insomnia continues for longer than 10 days, he should make an appointment with his health care provider for evaluation.

Patient Counseling for Insomnia

Patients with sleep disorders should be encouraged to practice good sleep hygiene measures. For some patients, these measures alone will resolve insomnia. If use of a nonprescription sleep aid is appropriate, dosing, appropriate duration, potential adverse effects, drug–drug interactions, and precautions or warnings should be explained carefully. In addition, patient education should include the signs and symptoms that indicate the need for follow-up with the provider. Taking a combination of pharmacologic products (i.e., prescription and nonprescription drugs, or drugs and dietary supplements) concomitantly to treat insomnia should be discouraged; this approach increases the risk of adverse effects. The box “Patient Education for Insomnia” lists specific information to provide patients.

Patient Education for Insomnia

The objectives of self-treatment are (1) to improve the duration and quality of sleep, (2) to reduce fatigue and drowsiness during the day, (3) to improve daytime functioning, and (4) to minimize adverse effects of

treatment. Carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes for most patients.

Disease Information

- Insomnia is difficulty getting enough sleep or trouble sleeping without interruption. Insomnia may be described as difficulty falling asleep, waking up too early, or waking up periodically during the night and not feeling rested during the day. Insomnia can cause fatigue and drowsiness during the day. Insomnia is *chronic* when it happens 3 times or more per week for 3 or more months. Insomnia can be caused by medical or psychiatric conditions, mental stress or excitement, or certain daytime and bedtime habits. If prescribed a medication that can exacerbate insomnia (e.g., a corticosteroid), talk with your health care provider about taking the medication in the morning.

Nondrug Measures

- See Table 46–3 for nondrug measures to prevent insomnia.
- Using principles of good sleep hygiene can help improve bad sleep habits and enhance quality sleep.
- If insomnia worsens or continues after 10 days of appropriate sleep hygiene plus CBT-I, seek medical attention.

Nonprescription Medications

- Age younger than 12 years or 65 years and older are exclusions for self-treatment of insomnia.
- Do not drive or operate machinery after taking sleep aids, including melatonin and valerian.
- Diphenhydramine is not expected to harm an unborn baby; however, you should not use diphenhydramine for sleep during pregnancy unless your health care provider recommends its use. It is important to tell your health care provider if you are pregnant or plan to become pregnant during treatment.
- Diphenhydramine may pass into breast milk and may harm a

nursing baby. Antihistamines also may slow breast milk production. Do not use this medication without medical advice if you are breastfeeding.

Diphenhydramine

- Establish a regular bedtime and take diphenhydramine 30 minutes before you want to go to sleep. Do not take more than 50 mg of diphenhydramine each night.
- After 3 nights of improved sleep, skip taking the medication for 1 night to see if the insomnia is resolved.
- Longer use of diphenhydramine will cause tolerance to the medication's sleep-inducing effects but not necessarily to its side effects. If your insomnia persists, you may have an underlying disorder.
- Note that diphenhydramine can cause morning grogginess or excessive sedation, dry mouth, blurred vision, constipation, and difficulty urinating (particularly in older men).
- Do not take diphenhydramine with alcohol; alcohol can increase the effects of the medication on the central nervous system. Alcohol also disrupts the sleep cycle.
- Do not combine use of diphenhydramine with prescription sleep aids.
- Consult your health care provider before taking diphenhydramine with other medications.

Evaluation of Patient Outcomes for Insomnia

Successful outcomes include decreased sleep-onset latency, improved sleep quality, and decreased daytime fatigue and drowsiness. The patient should be advised to seek medical evaluation if sleep has not improved in 10 days.

Key Points for Insomnia

- Refer patients with chronic insomnia or sleep disturbance caused by an underlying disorder for medical evaluation.
- Advise patients who are eligible for self-treatment to contact their health care provider if symptoms worsen or do not improve after 10 days.
- Counsel patients with insomnia about nondrug measures such as good sleep hygiene (Table 46–3).
- Refer children younger than 12 years, pregnant or breastfeeding women, and adults 65 years or older with insomnia to their health care provider.
- Advise patients about the different dosage forms of nonprescription sleep aids so they can select a product best suited for them.
- Advise patients that evidence to support the use of diphenhydramine is lacking and that its benefits are likely similar to its harms.
- Counsel patients on the adverse effects of diphenhydramine and, if applicable, other sleep aids, particularly next-day sedation, drowsiness, and the additive CNS depressant effects of alcohol and other sedating drugs.
- Advise patients taking a nonprescription sleep aid that contains diphenhydramine to avoid taking other oral drugs that contain this agent.
- Advise patients against combining the use of oral and topical diphenhydramine products.
- Advise patients to discuss the potential risks and benefits of complementary therapies with their health care provider before they select an agent.

Drowsiness and Fatigue

Drowsiness or fatigue may be acute in onset or chronic and can increase the risk of occupational or motor vehicle accidents, as well as adversely impact productivity, mood, and overall health.³¹ Evidence indicates an increased incidence of sleep-related crashes in young drivers who report an average of less than 6 hours of sleep per night.³²

Caffeine is the most frequently used CNS stimulant in the world to treat drowsiness or fatigue. Men and women consume an average of 196 mg daily and 151 mg daily, respectively, through ingestion of coffee, tea, and soft drinks. Youths’ daily consumption of caffeine is lower than that of adults. Caffeine consumption averaged 61 mg in those ages 14–19 years, 26 mg in those ages 9–13 years, and 15 mg in those ages 4–8 years.³³ Energy drinks are popular with adolescents and young adults. [Table 46–6](#) lists the caffeine content of commonly consumed beverages. Many nonprescription, prescription, and dietary supplements also contain caffeine. High total daily caffeine intake leads to adverse effects, withdrawal reactions, or, rarely, interactions with drugs.

TABLE 46–6 Caffeine Content in Common Dietary Sources		
Coffees, Teas, and Soft Drinks	Ounces	Caffeine Content (mg)
Brewed coffee	8	80–135
Brewed coffee, decaffeinated	8	3–4
Starbucks coffee, dark roast, tall	12	193
Starbucks coffee, dark roast, grande	16	260
Espresso	2	100
Instant coffee	8	65–100
Instant coffee, decaffeinated	8	2–3
Brewed tea, U.S. brands	8	40
Brew Dr. Kombucha	14	<15

Coffees, Teas, and Soft Drinks	Ounces	Caffeine Content (mg)
Snapple Iced Tea, flavored	8	31.5
Mountain Dew	12	55
Diet Coke	12	45.6
Coca-Cola Classic	12	34
Dr. Pepper	12	41
Dark chocolate	1	20

Note: The listed caffeine content for the brewed coffees and teas may vary according to brewing methods. The caffeine content in kombucha drinks may vary according to the number of days of fermentation.

Pathophysiology of Drowsiness and Fatigue

Daytime drowsiness and fatigue are caused most often by *inadequate sleep*, that is, sleep of both insufficient duration and quality. The degree of sleepiness is determined by two factors that regulate sleep and wakefulness: (1) a homeostatic process involving an increase in sleepiness as time since the most recent period of sleep increases and (2) a circadian process by which the master biological clock in the suprachiasmatic nucleus varies alertness over the course of the 24-hour day.³⁴ Other possible contributing factors include the use of CNS depressants, such as antihistamines, antipsychotics, anticonvulsants, and opioids. Dopamine agonists, antibiotics, and antihypertensive agents also may increase the risk of drowsiness. Increased susceptibility to the sedating effects of these agents can be particularly troublesome in older adults. Other etiologies include depression, cancer, anemia, hypothyroidism, chronic pain, overexertion, or inconsistencies in diet and exercise.³¹

Clinical Presentation of Drowsiness and Fatigue

The subjective experience of sleepiness includes feeling foggy or woozy, being responsive but not fully alert, and having dream-like thoughts. Patients may report a moderate to high chance of dozing off at inappropriate or dangerous

times, such as at work, in public, or while driving. Self-reported measures of sleepiness include the Stanford Sleepiness Scale and the Epworth Sleepiness Scale.^{31,35,36}

Treatment of Drowsiness and Fatigue

Treatment Goals

The goal in treating daytime drowsiness and fatigue is to identify and eliminate the underlying cause, thereby improving mental alertness and productivity. The algorithm in [Figure 46–2](#) outlines the approach to self-treatment.

General Treatment Approach

Many consumers use dietary sources of caffeine to self-treat occasional symptoms of fatigue and drowsiness. Nonprescription caffeine-containing products also may be used. Caffeine as a supplement, or in dietary form, is not a substitute for adequate sleep. Before recommending any caffeine-containing nonprescription product, the health care provider should rule out any drug-induced cause of daytime drowsiness and fatigue. If symptoms are chronic, especially with 7–8 hours of sleep, medical referral is indicated.

Nonpharmacologic Therapy

Good sleep hygiene principles should be emphasized ([Table 46–3](#)).

Pharmacologic Therapy

Caffeine inhibits phosphodiesterase, leading to increased levels of 3',5' cyclic adenosine monophosphate. This effect plays a role in preventing apnea. Caffeine also is a CNS stimulant that increases sensitivity of the medullary respiratory center to carbon dioxide, stimulates central inspiratory drive, and enhances contraction of skeletal muscles including the diaphragm.³⁷ Patients will benefit from increased alertness at moderate doses, but they also may experience unfavorable stimulant effects such as decreased fine motor coordination, headache, nervousness, and dizziness. More significant adverse effects include anxiety, irritability, insomnia, and tachycardia.^{37,38}

The stimulant effects of caffeine may be felt 15 minutes after a dose, and caffeine reaches peak concentration in 30–120 minutes. It has a volume of distribution of 0.6 L/kg in adults. Caffeine is metabolized in the liver by the CYP1A2 isoenzyme; active metabolites include theophylline. The elimination half-life of caffeine is about 5 hours in adults and children older than 9 years.^{37,38}

Caffeine is the only FDA-approved nonprescription stimulant. [Table 46–7](#) lists selected trade-name products that contain caffeine. The labeled dosages of approved nonprescription supplements for adults and children 12 years and older is 100–200 mg every 3–4 hours as needed. Caffeine is marketed for occasional use to help restore mental alertness or wakefulness.³⁹

TABLE 46–7 Selected Caffeine-Containing Products	
Trade Name	Caffeine Content (mg) per Unit
Nonprescription Caffeine-Only Products	
NoDoz Maximum Strength	200
Vivarin	200
Nonprescription Combination Products	
Excedrin Migraine	65
Midol Complete Caplets	60
Prescription Combination Products	
Cafergot	100
Fioricet	40
Fiorinal	40

Note: Information is not all inclusive. Products may have changed formulations or caffeine content since time of publication.

Tolerance to the effects of caffeine on the respiratory and cardiovascular

systems is common. Habitual caffeine drinkers who routinely consume as little as 100–200 mg daily and abruptly discontinue caffeine may experience mild signs and symptoms of withdrawal. Symptoms include headache, fatigue, decreased concentration, and irritability.⁴⁰

An exaggerated pharmacologic effect can occur when nonprescription caffeine is combined with dietary sources, or with prescription or nonprescription medications containing caffeine. For example, caffeine may reduce the clearance of theophylline, causing additive sympathetic effects such as an increased heart rate. The CYP1A2 isoenzyme can be induced or inhibited by other drugs. The routine use of high dosages of caffeine (400 mg daily) could theoretically saturate the binding sites and increase the risk of interactions with drugs that share this metabolic pathway. Cigarette smoking increases the clearance of caffeine by 56%.⁴¹ Individuals who are quitting smoking should be counseled to reduce their caffeine intake by half.⁴² Conversely, hormonal contraceptives and ciprofloxacin can inhibit the CYP1A2 isoenzyme. The clinical significance of these interactions is unknown, but patients taking these drugs should be cautioned to moderate their use of caffeine. Clinically significant drug interactions with caffeine are listed in [Table 46–8](#).⁴³ Genetic polymorphisms at CYP1A2 and adenosine receptors also may influence response to caffeine.

TABLE 46–8 Selected Clinically Significant Drug Interactions With Caffeine

Interacting Drugs or Drug Classes	Description	Monitoring Recommendation
Adenosine	Caffeine may diminish the therapeutic effect of adenosine.	Monitor for decreased effect of adenosine if patient is consuming caffeine. Many cardiac facilities instruct patients to avoid caffeine 12–24 hours prior to nuclear stress tests.
Atomoxetine	Atomoxetine may increase the hypertensive or tachycardic effect of caffeine.	Monitor therapy.
Cannabinoids (except cannabidiol)	These products may increase the tachycardic effect of	Monitor therapy.

Interacting Drugs or Drug Classes	Description	Monitoring Recommendation
	caffeine.	
Ciprofloxacin (systemic)	Ciprofloxacin may increase serum concentration of caffeine.	Monitor therapy.
Linezolid	Linezolid may enhance the hypertensive effect of caffeine.	Reduce initial doses of caffeine, and closely monitor blood pressure.
Lithium	Caffeine may decrease the serum concentration of lithium.	Monitor therapy.
Norfloxacin	Norfloxacin may increase the serum concentration of caffeine.	Monitor therapy.
Theophylline	Caffeine may increase the plasma concentration of theophylline.	Avoid concomitant use of caffeine or maintain consistent intake. Monitor theophylline trough concentrations.
Tizanidine	Caffeine may increase the serum concentration of tizanidine.	Avoid concomitant use when possible. If unavoidable, initiate tizanidine at 2 mg and increase in 2–4 mg increments according to patient response. Monitor for adverse reactions.
Tobacco (smoked)	Tobacco may decrease serum concentration of caffeine.	Monitor therapy.

Source: [Reference 43](#).

Patients who take monoamine oxidase inhibitors or have existing coronary

heart disease, uncontrolled hypertension, or preexisting arrhythmias should be counseled to avoid nonprescription caffeine-containing preparations and to moderate their intake of dietary caffeine. The consumption of coffee may lead to dose-related increases in blood pressure. A systematic review identified two cohort studies of patients receiving greater than 180 mg or greater than 200 mg caffeine per day, but less than 400 mg per day. An increase in blood pressure was not observed with these quantities. However, an analysis of 13 case-control studies showed an increased risk of coronary heart disease with daily intake of 275 mg or higher.⁴⁰

Caffeine has dose-related benefits for both rested and fatigued patients. After sleep deprivation, caffeine doses of 200–600 mg can improve psychomotor performance, alertness, and reaction time.⁴⁴ Cognitive function and driving performance were evaluated in participants receiving caffeine 200 mg (n = 50) or placebo (n = 50) after a 3-day washout period. Both brake reaction time and change in position of car were measured. Participants who received caffeine performed better on the Shifting Attention Test and had a shorter brake reaction time ($P = .03$ and $P = .048$, respectively).⁴⁵

The use of caffeinated coffee to counter the effects of excessive alcohol ingestion is a common practice. Although the combination of energy drinks or caffeine with alcohol increases alertness and reduces alcohol-related fatigue, it does not reverse alcohol-induced deficits on simple psychomotor tasks.⁴⁶ In 2010, FDA issued warning letters to manufacturers of caffeinated alcoholic beverages that they were in violation of the Federal Food, Drug, and Cosmetic Act because the combination of the two substances is not approved nor generally recognized as safe.⁴⁷

Patients should be cautioned about excessive consumption of caffeine in weight-loss supplements and energy sports drinks. Natural caffeine, other methylxanthines, and caffeine-containing herbs such as guarana, green tea, yerba mate, and kola nut are common ingredients in products marketed to young consumers for energy or weight loss.³⁸ The caffeine content is not always listed on the label of energy drinks. **Table 46–9** lists the amount of caffeine contained in selected weight-loss dietary supplements and sports energy drinks.

TABLE 46–9 Caffeine Content in Selected Dietary Supplements and Energy Drinks

Trade Name	Caffeine Content per Serving (mg)
Dietary Supplements	
Dexatrim Max Daytime Appetite Control	200
Pro Clinical Hydroxycut ^a	200
Energy Drinks^b	
5-hour Energy (regular strength)	200 ^c
Monster Energy	80 ^d
Red Bull	80 ^e
Rockstar Xduration	300

Note: Data are not all inclusive. Products may have changed formulations or caffeine content since time of publication.

^a Also contains Hydroxycut Blend 441 mg (robusta coffee extract, apple cider vinegar, plum, baobab extract, and cardamom).

^b Caffeine content based on serving size and strength sold.

^c Also contains taurine, glucuronic acid, malic acid, N-acetyl L-tyrosine, L-phenylalanine, and citicoline.

^d Also contains Monster Energy Blend (glucose, taurine, L-carnitine, inositol, maltodextrin).

^e Also contains taurine.

Product Selection Guidelines

Special Populations

Caffeine freely crosses the placenta and passes through breast milk.^{48,49} The American College of Obstetricians and Gynecologists has concluded that moderate caffeine consumption (defined by the organization as less than 200 mg daily) does not contribute to miscarriages or preterm births.⁴⁸ Total daily

caffeine intake should be limited to less than 200 mg during pregnancy; however, a systematic analysis supports use up to 300 mg daily.⁴⁰ The American Academy of Pediatrics considers usual dietary amounts of caffeine (defined by the organization as 300 mg or less daily) compatible with breastfeeding.⁴⁹ Infants unable to metabolize caffeine or those who receive large quantities of caffeine through breast milk may have symptoms of nervousness, increased heart rate, sleeplessness, poor feeding, and irritability. Nursing women should consume caffeine only in small to moderate amounts (2–3 cups daily), preferably right after breastfeeding to minimize effects on the infant.

Children are more susceptible to the cardiovascular and CNS adverse effects of caffeine because of their lower body weight. Four of five controlled trials from a systematic review of children and/or adolescents using 1–5 mg/kg of caffeine found a statistically significant increase in blood pressure. Although daily caffeine intake of 2.5 mg/kg is considered safe for this age group, blood pressure increases were observed at doses below and above this threshold.⁴⁰ Use of nonprescription caffeine products is not indicated in children younger than 12 years.

Patient Factors

Health care providers should consider age, comorbid conditions, and concomitant medications when recommending treatment for drowsiness and fatigue.

Patient Preferences

Patients may prefer to consume caffeine as beverages rather than as tablets or capsules. If they choose oral formulations of caffeine, they also should be aware of the caffeine content of any consumed beverages.

Complementary Therapies

Ginseng is used frequently to boost physical and mental energy and to produce a sense of well-being. A review of randomized controlled trials reveals contradictory scientific evidence to support these claims (see [Chapter 51](#)). Caffeine-containing dietary supplements that patients may be using include kola nut, guarana, and yerba mate. Soy isoflavones and black cohosh are marketed in combination with caffeine, green tea, and yerba mate to boost

energy and manage fatigue in women who are postmenopausal. Ingredients purported to counteract fatigue that are often found in sports energy drinks include taurine and guarana, although the amounts are unlikely to produce either therapeutic or adverse effects.

Assessment of Drowsiness and Fatigue: A Case-Based Approach

When assessing a patient with a complaint of daytime drowsiness, the health care provider should determine the cause of fatigue. Evaluating the patient's medical or psychiatric problems, current medication use, dietary caffeine consumption, sleep patterns, and lifestyle will help in determining the underlying cause. Because data supporting the efficacy of caffeine are lacking and adverse effects are associated with recommended and excessive dosages, health care providers should recommend improved sleep hygiene and lifestyle modifications or medical referral before they recommend the use of a caffeine-containing product.

Case 46–2 provides an example of the assessment of a patient with drowsiness and fatigue.

Algorithm: Drowsiness and Fatigue

FIGURE 46–2 Self-care of drowsiness and fatigue. HCP = Health care provider.

Case 46–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential	

Relevant Evaluation Criteria	Scenario/Model Outcome
information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient requests advice on choosing a nonprescription product to avoid daytime sleepiness. She reports that she sleeps fairly well, but by 1 or 2 PM each day at work, she is drowsy and sometimes nods off at her desk. She estimates this problem has been occurring for about 2 months now.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	She spends most of her work day on the phone, calling her patients or meeting with them in-person at the center. She finds it hard to sit for most of the day at her desk and is stressed out because she is behind on social work progress notes.
c. Description of the patient's/caregiver's efforts to relieve the symptoms	The patient starts her day with 2 cups of instant coffee and, sometime after 12 pm, purchases 2 Diet Cokes from the vending machine at the clinic.
d. Patient's identity	Samantha Glines
e. Patient's age, gender, height, and weight	55 years old, female, 5 ft 4 in., 138 lb
f. Patient's occupation	Social worker
g. Patient's dietary habits	Normal diet. Patient is working to reduce her daily salt consumption from food.
h. Patient's sleep habits	Patient reports her sleep is pretty good at nighttime, unless she comes home from work and "crashes" first.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	<i>Depression:</i> sertraline 150 mg daily (current dose for 1 year); <i>Focal seizures:</i> levetiracetam extended-release 1000 mg daily (dose increased 2 months ago); no dietary supplements.
j. Allergies	No known drug allergies.
k. History of other adverse	None

Relevant Evaluation Criteria	Scenario/Model Outcome
reactions to medications	
I. Other (describe) -----	n/a
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Daytime fatigue
3. Identify exclusions for self-treatment (Figure 46-2).	Medication-induced drowsiness.
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer Samantha to an appropriate health care provider. (2) Recommend self-care with a nonprescription stimulant and nondrug measures. (3) Recommend self-care until Samantha can see an appropriate provider. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Samantha needs to see her health care provider because she has had a medication dose adjustment that corresponds with the onset of her daytime sleepiness.
6. Describe the recommended therapeutic approach to the patient or	"You should make an appointment to see your health care provider."

Relevant Evaluation Criteria	Scenario/Model Outcome
caregiver.	
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	“Because this problem of fatigue may be caused by the change in the dose of your medication for seizures, you should make an appointment with your health care provider for a physical examination. Stimulant medication is not indicated at this time because your provider will have to decide on the best method of treatment. Even before you see your health care provider, you should reduce your intake of soda drinks and coffee, and begin sleep hygiene measures.”
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	Criterion does not apply to this case.
Solicit follow-up questions from the patient or caregiver.	“Can I switch from Diet Coke to energy drinks instead?”
Answer the patient’s or caregiver’s questions.	“Energy drinks often do not list all of the ingredients and their quantities. It would be best that you do not use these products and wait to discuss your daytime drowsiness with your health care provider.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact the patient in 1-2 days to be sure she made an appointment for medical care.

Key: n/a = Not applicable.

Patient Counseling for Drowsiness and Fatigue

Counseling on the treatment of drowsiness and fatigue should focus on practicing good sleep hygiene and eliminating factors that interfere with normal sleep. If a caffeine product is indicated, the health care provider should review dosage guidelines with the patient and emphasize the potential adverse effects and drug interactions. The patient should be counseled on symptoms of excessive caffeine ingestion, such as irritability, tremor, rapid pulse, dizziness, and heart palpitations. Regular users of caffeine also should be counseled on withdrawal symptoms such as headache and anxiety, which can occur if caffeine from any source is stopped abruptly. The box “Patient Education for Drowsiness and Fatigue” lists information to provide patients.

Evaluation of Patient Outcomes for Drowsiness and Fatigue

Successful outcomes include daytime alertness, increased productivity, and peak performance with respect to psychomotor tasks and cognitive function, including attention and concentration. An individual should seek medical evaluation if, after 7–10 days, drowsiness and fatigue persist despite the limited use of caffeine and the establishment of good sleep hygiene.

Patient Education for Drowsiness and Fatigue

The objective of self-treatment is to maintain wakefulness. For most patients, improved sleep hygiene will help ensure optimal therapeutic outcomes. If the patient insists on taking a caffeine-containing product, carefully following product instructions and the self-care measures listed here will help ensure optimal therapeutic outcomes for most patients.

Disease Information

- Symptoms of drowsiness and fatigue often include feeling foggy, woozy, and/or not fully alert, and having dream-like thoughts.

Nondrug Measures

- Practice principles of good sleep hygiene (Table 46–3).
- If drowsiness or fatigue persists or recurs, consult your health care provider.

Nonprescription Medications

- Do not exceed the recommended caffeine dose of 100–200 mg every 3–4 hours as needed. Note that higher doses of caffeine may cause side effects, and chronic use may result in tolerance as well as withdrawal symptoms upon abrupt discontinuation.
- Do not use caffeine tablets in combination with coffee or other caffeinated products, including dietary supplements.
- Discuss safe daily caffeine consumption with your health care provider if you are pregnant or breastfeeding.
- Do not give caffeine to children younger than 12 years.
- If you are taking atomoxetine or ciprofloxacin, consult your health care provider before using caffeine-containing products.
- If you have a history of peptic ulcer disease, psychiatric disorders, symptomatic heart disease, or uncontrolled hypertension, consult your health care provider before using caffeine products.

When to Seek Medical Attention

- Seek medical attention immediately if the following symptoms of caffeine toxicity occur at the same time:
 - Increases in heart rate and blood pressure
 - Headache
 - Symptoms of anxiety and insomnia
 - Increase in hand tremor

Key Points for Drowsiness and Fatigue

- Advise patients that caffeine appears to be safe and effective in low to moderate doses in the diet, as well as for occasional use as a nonprescription supplement during completion of tasks of short duration when enhanced alertness is desired.
- Instruct patients that caffeine is most effective when taken intermittently at dosages of 100–200 mg every 3–4 hours as needed.
- Pregnant or nursing women, children younger than 12 years, patients with heart disease, and patients with anxiety disorders should avoid use of caffeine.
- Health care providers should be aware of the patient's use of prescription and nonprescription medications and dietary supplements that contain caffeine, as well as the patient's dietary consumption of caffeine.
- Adverse effects of caffeine are more likely to occur in occasional users and patients of advanced age.
- Advise patients taking daily dosages of caffeine higher than 200 mg about possible drug interactions.
- Counsel patients against use of dietary supplements to increase energy or decrease fatigue.

Chapter 47: Tobacco Cessation

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In 1982, the U.S. Surgeon General C. Everett Koop stated that cigarette smoking was the “chief, single, avoidable cause of death in our society and the most important public health issue of our time.”¹ This statement remains true nearly 4 decades later. In the United States, cigarette smoking is the leading known cause of preventable death,² responsible for an estimated 480,000 deaths each year.³ In addition to lives lost, the economic impact of smoking is enormous, costing society approximately \$300 billion annually for smoking-attributable health expenditures and lost productivity.³

The negative effects of smoking are both well established and well publicized. Although cigarette smoking among U.S. adults has decreased significantly, data reported in 2017 show that an estimated 34.3 million adult Americans (14% of the overall population—15.8% of males and 12.2% of females) still smoked either every day or some days.⁴ Tobacco products have evolved to now include combustible, noncombustible, and electronic products. In 2017, the number of U.S. adults using any of these products jumped to roughly 47.4 million adults (19.3%).⁴ Among those who use tobacco products, nearly 20% (9.0 million) use two or more tobacco products.⁴ The prevalence of smoking cigarettes varies in accordance with sociodemographic factors including gender, race/ethnicity, education level, age, and socioeconomic status. The prevalence of smoking in the United States was highest among non-Hispanic American Indians/Alaska Natives (24%) and lowest among non-Hispanic Asians (7.1%). Smoking is more common among people ages 45–64 years (16.5%) and those living below the federal poverty level (21.4%).⁴ Smoking also is more prevalent for those with less than a post-secondary education, ranging from 18.7% in high school graduates to 36.8% in those who have completed a General Educational Development test).⁴ The median prevalence of smoking varies by state, with Utah exhibiting the lowest prevalence at 8.9% and West Virginia exhibiting the highest at 26%.⁵

The U.S. Food and Drug Administration (FDA) developed new cigarette health warnings in 2020 that are designed to promote greater public understanding of the negative health consequences of cigarette smoking. Beginning October 16, 2021, the warnings must appear prominently on cigarette packages and in advertisements. On the front and rear panels of cigarette packages, a warning

will occupy the top 50% of a panel. In cigarette advertisements, the warnings will occupy at least 20% of the top portion of an advertisement. Once implemented, the new warnings must be randomly and equally displayed and distributed on cigarette packages and rotated quarterly in cigarette advertisements.^{6,7}

Although tobacco control efforts have helped reduce the rate of cigarette smoking, the use of e-cigarettes, or electronic nicotine delivery systems (ENDS), is on the rise, and the statistics are alarming. Frequent use of ENDS products, defined as use that occurred more often than 20 days in the past 30 days, increased from 20% in 2017 to 27.7% in 2018 among current high school users.⁸ Data from a 2019 survey showed a further increase of 34.2% in high school students; the data also showed 18% of middle school students had used ENDS.⁹ From 2018 to 2019, use of e-cigarettes in the past 30 days by high school students increased from 20.8%⁸ to 27.5%.⁹ The 2018 survey data also showed that 4.9% of middle schoolers had used an e-cigarette in the past 30 days⁸; in 2019 this usage had increased to 10.5%.⁹ Literature also has shown that 43.9% of youth who had used e-cigarettes but not conventional cigarettes had an intention to smoke conventional cigarettes, and 21.5% of those who had never used either type of cigarette had an intention to smoke conventional cigarettes.¹⁰

Pathophysiology of Tobacco Use and Dependence

In 1988, the U.S. Surgeon General released a landmark report in which the authors concluded that tobacco products are effective nicotine delivery systems capable of inducing and sustaining chemical dependence.¹¹ The primary criteria used to categorize nicotine as an addictive substance were its (1) psychoactive effects, (2) use in a highly controlled or compulsive manner, and (3) reinforcement of behavioral patterns of tobacco use. The underlying pharmacologic and behavioral processes associated with tobacco dependence are considered to be similar to those that determine addiction to drugs such as heroin and cocaine.¹¹

As with other addictive substances (e.g., opiates, cocaine, amphetamines), nicotine stimulates the mesolimbic dopaminergic system in the midbrain,

inducing pleasant or rewarding effects that promote continued use.¹² This effect is referred to as the *dopamine reward pathway*. Nicotine binds to the $\alpha_4\beta_2$ nicotinic cholinergic receptors in the ventral mental area of the brain, triggering the release of dopamine in the nucleus accumbens. Psychosocial, behavioral, genetic, and environmental factors also play an important role in establishing and maintaining dependence.^{12,13} For example, smoking commonly is associated with specific activities such as driving, talking on the telephone, eating, drinking coffee or alcohol, and being around others who smoke. Over time, the habitual use of cigarettes under these circumstances can lead to the development of smoking routines that can be difficult to break. Indeed, specific environmental situations can become powerful conditioned stimuli or cues associated with smoking that are capable of triggering “automatic” smoking patterns.¹²

Tobacco use dramatically increases one’s odds of dependence, disease, disability, and death. Cigarettes are carefully engineered and heavily marketed products. For example, although the design of cigarettes and other tobacco products has evolved over the past 5 decades (e.g., filtered, menthol, low-tar, “light” cigarettes; e-cigarettes; dissolvable tobacco), overall disease risk has not been reduced among smokers.¹³ The tobacco industry spends nearly \$20 to market its products for every \$1 that states spend on tobacco control.¹⁴ Cigarettes are the *only* marketed consumable product that, when used persistently, will kill half or more of its users.¹⁵

The Environmental Protection Agency (EPA) classifies cigarette smoke as a Class A carcinogen (i.e., a carcinogen with no safe level of exposure for humans). Cigarette smoke is a complex mixture of thousands of compounds—including nitrogen, carbon monoxide, ammonia, hydrogen cyanide, benzene, and nicotine—in gaseous and particulate phases. The particulate fraction, excluding the nicotine and water components, is collectively referred to as *tar*. Numerous carcinogens, including polycyclic aromatic hydrocarbons (PAHs) and nitrosamines, have been identified in the tar fraction of tobacco smoke.^{13,16}

Nicotine, the addictive component of tobacco, is distilled from burning tobacco and then carried in tar droplets to the small airways of the lung, where it is absorbed rapidly into the arterial circulation and distributed throughout the body. Nicotine readily penetrates the central nervous system and is estimated to reach the brain within seconds after inhalation.¹⁷ Nicotine binds

to receptors in the brain and other organs, inducing a variety of predominantly stimulatory effects on the cardiovascular, endocrine, nervous, and metabolic systems.¹⁸ Pharmacodynamic effects associated with nicotine administration include arousal and increases in the heart rate and blood pressure. In the brain, smoking leads to the activation of nicotinic cholinergic receptors and release of numerous neurotransmitters, which induce a range of effects such as pleasure (dopamine), arousal (acetylcholine and norepinephrine), cognitive enhancement (acetylcholine), appetite suppression (dopamine, norepinephrine, and serotonin), learning and memory enhancement (glutamate), mood modulation (serotonin), and reduction of anxiety and tension (beta-endorphin and gamma-aminobutyric acid).^{12,13,17}

Clinical Presentation of Tobacco Use and Dependence

Most chronic tobacco users develop tolerance to the effects of nicotine, and abrupt cessation precipitates symptoms of nicotine withdrawal.¹² The symptoms and their severity vary from person to person but generally include irritability, frustration, anger, anxiety, depression, difficulty concentrating, impatience, insomnia, and restlessness.^{19,20} Other symptoms that patients may report include cravings, impaired performance, constipation, cough, dizziness, and increased dreaming. Typically, the physiologic symptoms of nicotine withdrawal manifest within the first 1–2 days, peak within the first week, and gradually dissipate over 2–4 weeks.²⁰ Increased appetite and weight gain may persist for 6 or more months after quitting.¹⁹

According to reports issued by the U.S. Surgeon General in 2004,² 2010,¹³ and 2014,³ smoking adversely affects nearly every organ system in the body and plays a causal role in the development of numerous diseases, including many cancers (**Table 47–1**). Furthermore, smoking cigarettes with lower machine-measured yields of tar and nicotine provides no clear benefit to health. Involuntary exposure to secondhand smoke, which includes the smoke emanating from a cigarette and then exhaled by the smoker, is associated with adverse health effects in nonsmokers, including cardiovascular disease, respiratory disease, and lung cancer.²¹ Even low levels of exposure, such as secondhand smoke exposure, are associated with rapid increases in endothelial dysfunction and inflammation, which lead to acute cardiovascular

events and thrombosis.¹³ In children, secondhand smoke exposure can increase the risk of ear infections; precipitate more frequent and severe asthma attacks; worsen respiratory symptoms (e.g., coughing, sneezing, shortness of breath); increase the risk of respiratory infections; and increase the risk for sudden infant death syndrome (SIDS).²¹ There is no risk-free level of exposure to tobacco smoke.^{13,22}

TABLE 47-1 Health Consequences of Smoking

Cancer

Acute myeloid leukemia
Bladder
Breast
Cervical
Colorectal
Esophageal
Gastric
Kidney
Laryngeal
Liver
Lung
Oral cavity and pharyngeal
Pancreatic
Prostate

Cardiovascular Diseases

Abdominal aortic aneurysm
Coronary heart disease (e.g., angina pectoris, ischemic heart disease, myocardial infarction)
Cerebrovascular disease (e.g., transient ischemic attacks, stroke)
Peripheral arterial disease

Pulmonary Diseases

Acute respiratory illnesses
 Upper respiratory tract disease (e.g., rhinitis, sinusitis, laryngitis, pharyngitis)
 Lower respiratory tract disease (e.g., bronchitis, pneumonia)
Chronic respiratory illnesses
 Chronic obstructive pulmonary disease
 Respiratory symptoms
 Exacerbation of asthma
 Reduced lung function
 Tuberculosis

Reproductive Effects

Reduced fertility in women
Pregnancy and pregnancy outcomes
 Premature rupture of membranes

Placenta previa
Placental abruption
Preterm delivery
Low infant birth weight
Ectopic pregnancy
Infant mortality
Sudden infant death syndrome (SIDS)
Erectile dysfunction

Ophthalmic Effects

Cataract
Neovascular and atrophic forms of age-related macular degeneration

Other Effects

Diabetes (30%–40% higher risk for active smokers, with a dose–response relationship between the number of cigarettes smoked and this risk)
Osteoporosis (reduced bone density in postmenopausal women, with increased risk of hip fracture)
Periodontitis
Peptic ulcer disease (in patients infected with *Helicobacter pylori*)
Rheumatoid arthritis
Surgical outcomes—suboptimal
 Poor wound healing
 Respiratory complications

Source: [References 2, 3, and 16](#).

Tobacco smoke interacts with medications through pharmacokinetic or pharmacodynamic mechanisms that can lead to reduced therapeutic efficacy or, less commonly, increased toxicity. Most of the pharmacokinetic interactions are the result of induction of hepatic cytochrome P450 (CYP) enzymes (primarily the CYP1A2 isoenzyme) by PAHs present in tobacco smoke.²³ Induction of the CYP1A2 isoenzyme can increase the hepatic metabolism of certain drugs ([Table 47–2](#)), potentially resulting in a reduced therapeutic response or a need for higher dosages in smokers; conversely, the dosages of some drugs might need to be reduced in patients who quit smoking.²³ Similarly, the clearance of caffeine is significantly increased (by 56%) in smokers. After cessation, ex-smokers who drink caffeinated beverages should be advised to decrease their usual caffeine intake to avoid higher levels of caffeine, which may induce symptoms similar to nicotine withdrawal.

TABLE 47-2 Drug Interactions With Tobacco Smoke

Drug/Class (Trade Name)	Mechanism of Interaction and Effects
Pharmacokinetic Interactions	
Alprazolam (Xanax)	Conflicting data on significance, but possible decreased plasma concentrations (up to 50%); decreased half-life (35%).
Bendamustine (Treanda) ^a	Metabolized by CYP1A2. Manufacturer recommends using with caution in smokers owing to likely decreased bendamustine concentrations, with increased concentrations of its two active metabolites.
Caffeine ^a	Increased metabolism (induction of CYP1A2); increased clearance (56%). Caffeine levels are likely increased after cessation.
Chlorpromazine (Thorazine)	Decreased AUC (36%) and serum concentrations (24%).
	Decreased sedation and hypotension possible in smokers; smokers may require increased dosages.
Clopidogrel (Plavix) ^a	Increased metabolism (induction of CYP1A2) of clopidogrel to its active metabolite.
	Clopidogrel's effects are enhanced in smokers (≥10 cigarettes/day): significant increased platelet inhibition, decreased platelet aggregation. Although improved clinical outcomes have been shown (smoker's paradox; may be dependent on CYP1A2 genotype); tobacco cessation should still be recommended in at-risk populations needing clopidogrel.
Clozapine (Clozaril) ^a	Increased metabolism (induction of CYP1A2); decreased plasma concentrations (18%).
	Increased levels may occur upon cessation; closely monitor drug levels and reduce dose as required to avoid toxicity.
Erlotinib (Tarceva) ^a	Increased clearance (24%); decreased trough serum concentrations (twofold).
Flecainide (Tambocor)	Increased clearance (61%); decreased trough serum concentrations (25%). Smokers may need increased dosages.
Fluvoxamine (Luvox) ^a	Increased metabolism (induction of CYP1A2); increased clearance (24%); decreased AUC (31%); decreased plasma concentrations (32%).
	Dosage modifications are not routinely recommended, but smokers may need

Drug/Class (Trade Name)	Mechanism of Interaction and Effects
	increased dosages.
Haloperidol (Haldol) ^a	Increased clearance (44%); decreased serum concentrations (70%); data are inconsistent; therefore, clinical significance is unclear.
Heparin	Mechanism unknown but increased clearance and decreased half-life. Smoking has prothrombotic effects.
	Smokers may need increased dosages due to PK and PD interactions.
Insulin, subcutaneous	Possible decreased insulin absorption secondary to peripheral vasoconstriction; smoking may cause release of endogenous substances that cause insulin resistance.
	PK and PD interactions are likely not clinically significant; smokers may need increased dosages.
Irinotecan (Camptosar) ^a	Increased clearance (18%); decreased serum concentrations of active metabolite, SN-38 (~ 40%), via induction of glucuronidation; decreased systemic exposure resulting in lower hematologic toxicity; may reduce efficacy.
	Smokers may need increased dosages.
Methadone	Possible increased metabolism (induction of CYP1A2, a minor pathway for methadone).
	Carefully monitor response upon cessation.
Mexiletine (Mexitil)	Increased clearance (25%; via oxidation and glucuronidation); decreased half-life (36%).
Nintedanib (OFEV)	Decreased exposure (21%) in smokers. No dose adjustment recommended; however, patients should not smoke during use.
Olanzapine (Zyprexa) ^a	Increased metabolism (induction of CYP1A2); increased clearance (98%), decreased serum concentrations (12%).
	Dosage modifications are not routinely recommended, but smokers may need increased dosages.
Pirfenidone (Esbriet)	Increased metabolism (induction of CYP1A2), decreased AUC (46%), and decreased plasma concentration (68%).
	Decreased exposure in smokers might alter efficacy profile.

Drug/Class (Trade Name)	Mechanism of Interaction and Effects
Propranolol (Inderal)	Increased clearance (77%, via side chain oxidation and glucuronidation).
Riociguat (Adempas) ^a	Decreased plasma concentrations (by 50%–60%).
	Smokers may require dosages higher than 2.5 mg 3 times a day; consider dose reduction upon cessation.
Ropinirole (Requip) ^a	Decreased maximum concentration (30%) and AUC (38%) in study with patients with restless legs syndrome.
	Smokers may need increased dosages.
Tacrine (Cognex) ^a	Increased metabolism (induction of CYP1A2); decreased half-life (50%); serum concentrations threefold lower.
	Smokers may need increased dosages.
Tasimelteon (Hetlioz) ^a	Increased metabolism (induction of CYP1A2); drug exposure decreased by 40%.
	Smokers may need increased dosages.
Theophylline ^a	Increased metabolism (induction of CYP1A2); increased clearance (58%–100%); decreased half-life (63%).
	Levels should be monitored if smoking is initiated, discontinued, or changed. Maintenance doses are considerably higher in smokers.
	Increased clearance with secondhand smoke exposure.
Tizanidine (Zanaflex)	Decreased AUC (30%–40%) and decreased half-life (10%) observed in male smokers.
Tricyclic antidepressants (e.g., imipramine, nortriptyline)	Possible interaction with tricyclic antidepressants in the direction of decreased blood levels, but the clinical significance is not established.
Warfarin	Increased metabolism (induction of CYP1A2) of R-enantiomer; however, S-enantiomer is more potent, and the effect on the international normalized ratio (INR) is inconclusive. Consider monitoring INR more closely upon smoking cessation.

Drug/Class (Trade Name)	Mechanism of Interaction and Effects
Pharmacodynamic Interactions	
Benzodiazepines (diazepam, chlordiazepoxide)	Decreased sedation and drowsiness, possibly caused by nicotine stimulation of central nervous system.
Beta blockers	Less effective antihypertensive and heart rate control effects, possibly caused by nicotine-mediated sympathetic activation.
	Smokers may need increased dosages.
Corticosteroids, inhaled ^a	Smokers with asthma may have less of a response to inhaled corticosteroids.
Hormonal contraceptives ^a	Increased risk of cardiovascular adverse effects (e.g., stroke, myocardial infarction, thromboembolism) in women who smoke and use oral contraceptives. Ortho Evra patch users have twofold increased risk of venous thromboembolism compared with oral contraceptive users, likely owing to increased estrogen exposure (60% higher levels).
	Risk increases with age and with heavy smoking (≥15 cigarettes per day) that is quite marked in women ≥35 years of age.
Serotonin 5-HT ₁ receptor agonists (triptans)	This class of drugs may cause coronary vasospasm; caution is indicated for use in smokers owing to possible unrecognized CAD.

Note: Many interactions between tobacco smoke and medications have been identified. In most cases, the tobacco smoke—not the nicotine—causes these drug interactions. Tobacco smoke interacts with medications through PK and PD mechanisms. PK interactions affect the absorption, distribution, metabolism, or elimination of other drugs, potentially causing an altered pharmacologic response. A majority of PK interactions with smoking are the result of induction of hepatic cytochrome P450 enzymes (primarily CYP1A2). PD interactions alter the expected response or actions of other drugs. The amount of tobacco smoking necessary to have an effect has not been established, and the assumption is that any smoker is susceptible to the same degree of interaction. Those exposed regularly to secondhand smoke may also be at risk.

^a Clinically significant interaction.

Key: AUC = Area under the curve; CAD = coronary artery disease; HT₁ = hydroxytryptamine (receptor) class 1; PD = pharmacodynamic; PK = pharmacokinetic.

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A significant pharmacodynamic drug interaction occurs between tobacco smoke and combination hormonal contraceptives (pills, patch, and ring). Data indicate that cigarette smoking substantially increases the risk of serious adverse cardiovascular events (e.g., stroke, myocardial infarction, thromboembolism) in women using oral contraceptives.^{24–28} This risk is markedly increased in women 35 years of age or older who smoke 15 or more cigarettes per day.²⁴ Accordingly, most experts consider use of hormonal contraceptives to be a contraindication in smokers and recommend use of an alternative form of contraception.^{25,28} Additional drug–smoking interactions, with their corresponding underlying mechanisms, are listed in [Table 47–2](#).²⁹ During the course of routine patient care, it is important to assess for potential drug and smoking interactions and to make appropriate adjustments to the medication regimen.

Smoking Cessation Treatment

The 2010 Surgeon General’s Report on the health benefits of smoking cessation outlined the numerous and substantial health benefits realized when patients quit smoking.³⁰ Some health benefits are incurred shortly after quitting (e.g., within 2 weeks–3 months), and others are incurred over time ([Figure 47–1](#)). On average, cigarette smokers die approximately 10 years earlier than nonsmokers; among those who continue smoking, at least half will eventually die of a tobacco-related disease. Quitting at the ages of 30, 40, 50, and 60 years results in a gain of 10, 9, 6, and 3 years of life, respectively.^{3,16} Consequently, although it is important to educate tobacco users that it is never too late to quit to achieve many of the associated health benefits, significant benefits to quitting earlier in life also should be emphasized.

FIGURE 47–1 Health benefits of smoking cessation. (Source: [References 2, 3,](#) and [16.](#))

Treatment Goals

Tobacco dependence is a chronic disease typically characterized by multiple failed attempts to quit before long-term cessation is achieved. Because tobacco use is a complex, addictive behavior, helping patients quit and preventing relapse are best achieved by combining appropriate pharmacotherapy with counseling.³¹ For any patient who uses tobacco, the primary goal is complete, long-term abstinence from all nicotine-containing products.

General Treatment Approach

Most smokers use no cessation treatments for their quit attempts, an approach known as quitting “cold turkey,”³² and approximately 95% of all attempts to quit using this method end in relapse.³¹ Yet decades of research clearly show that patients who receive assistance have increased odds of quitting. The 2008 U.S. Public Health Service clinical practice guideline for treating tobacco use and dependence³¹ presents evidence-based recommendations and effective strategies for health care providers who provide tobacco cessation counseling. Although even brief advice from a provider is associated with increased odds of quitting,^{31,33} more intensive counseling (longer and more frequent counseling sessions, or greater overall contact time) and use of pharmacotherapy (except in patients with exclusions for self-treatment with medications, as listed in [Figure 47–2](#)) result in increased quit rates. Two particularly effective types of counseling are practical counseling (behavior change counseling, including problem-solving and skills training) and social support delivered as part of the treatment.³¹

Patients who receive a tobacco cessation intervention from a provider, either nonphysician or physician, are 1.7 or 2.2 times, respectively, more likely to quit (and remain tobacco free at >5 months after cessation), than are patients who do not receive a provider’s intervention.³¹ Self-help materials are only slightly better than no provider intervention. Although the length of an intervention increases effectiveness, even minimal interventions (<3 minutes) increase cessation rates.³¹ In a meta-analysis of 46 studies, four or more intervention sessions were found to approximately double cessation rates.³¹

Although the use of pharmacotherapy substantially increases patients' chances of quitting, the addition of counseling further increases cessation rates by a factor of 1.4.³¹ Similarly, adding pharmacotherapy to counseling increases cessation rates. When medications are not contraindicated, cessation interventions should consist of pharmacotherapy (one medication or combination therapy) and counseling (see later under "Special Populations").³¹ Figure 47–2 outlines a self-treatment approach for tobacco cessation.

Nonpharmacologic Therapy

Helping Patients Quit: The 5 A's Approach (Comprehensive Counseling)

As delineated in the U.S. Public Health Service Clinical Practice Guideline for Treating Tobacco Use and Dependence,³¹ the five key components of comprehensive counseling for tobacco cessation are (1) asking patients whether they use tobacco, (2) advising tobacco users to quit, (3) assessing patients' readiness to quit, (4) assisting patients with quitting, and (5) arranging follow-up care. These steps are referred to as the "5 A's."

Ask About Tobacco Use

A key first step in the cessation process, and in all patient interactions, is asking about tobacco use. Because tobacco use is the primary known preventable cause of mortality in the United States and because tobacco smoke interacts with multiple medications, screening for tobacco use is crucial and should be a routine component of care. The following question can be used to identify all types of tobacco use, even for infrequent users: "Do you ever smoke or use any type of tobacco?" Specifically asking about e-cigarette use may be necessary; using the specific terms of "JUULing" or "vaping" or "pods" may be necessary for the user to identify their inhaled nicotine use. In clinic or hospital settings, tobacco use status should be considered a component of vital sign assessment and collected routinely, along with blood pressure, pulse, weight, temperature, and respiratory rate.³¹ In community pharmacies, tobacco use status should be assessed, documented in the patient profile, and reassessed periodically. Asking about exposure to secondhand smoke also should be considered.

Advise to Quit

All tobacco users should be advised to quit. The advice should be clear, strong, and personalized, yet delivered with sensitivity and in a tone of voice that communicates concern for the patient and a willingness to provide appropriate assistance with quitting when the patient is ready. When possible, primary care providers should individualize the message by linking their advice to the patient's health status, current medication regimen, personal reasons for wanting to quit, or the effect of tobacco on others. The following example highlights this approach: "Ms. Bettis, I see that you now are on two different inhalers for your emphysema. Quitting smoking is the single most important treatment for your emphysema and can improve how well your inhalers work. I strongly encourage you to quit, and I would like to help you."

Assess Readiness to Quit

Because many patients will not be ready to quit when they are first approached, it is important for providers to gauge each patient's readiness to quit before recommending a treatment regimen. Patients should be categorized as (1) not ready to quit in the next month; (2) ready to quit in the next month; (3) a recent quitter, having quit in the past 6 months; or (4) a former user, having quit more than 6 months ago.³¹ This classification defines the provider's next course of action, which is to provide counseling that is tailored to the patient's readiness to quit. The following approach is an example for a current smoker: "Mr. Crosby, what are your thoughts about quitting? Is this something that you might consider doing in the next month?" Counseling a patient who is ready to quit in the next month should differ from counseling a patient who is not considering quitting in the near future.

Assist With Quitting

Important elements of the assisting component of treatment include helping patients to make the decision to quit and to set a quit date within the next month if possible. Providers should be empathetic and acknowledge that quitting is a challenge for most patients. When asked to set a quit date in the next month, patients are sometimes reluctant. A follow-up question could be "What is the worst thing that could happen if you tried to quit now?" This allows patients to consider whether any barriers to quitting exist, whether their perceptions are disproportionate, and what they may learn by attempting

to quit. Accordingly, the goal is to help maximize each patient's chances of success by designing an individualized treatment plan.

All patients attempting to quit should be encouraged to use pharmacotherapy combined with counseling. This combination will yield higher quit rates than either approach alone, except in special circumstances or in specific populations for which adequate evidence of the combined method's effectiveness is lacking (pregnant women, smokeless tobacco users, people who smoke fewer than 10 cigarettes per day, and adolescents).³¹ Counseling interventions, which focus on promoting behavior change and enhancing adherence with medication regimens, may include individualized counseling (e.g., in person or by telephone), a group cessation program, an internet-based program, or a combination of these approaches.

Arrange Follow-up Counseling

Because the patient's ability to quit increases substantially when multiple counseling interactions are provided, arranging follow-up counseling is an important, yet typically neglected, element of treatment for tobacco dependence. Follow-up contact should occur soon after the quit date, preferably during the first week. Follow-up does not have to be done in person and could be performed by telephone or electronic communication. A second follow-up contact is recommended within the first month after quitting.²⁸ Additional follow-up contacts should occur periodically to monitor patient progress (including adherence to pharmacotherapy regimens) and to provide ongoing support. Quit rates at 5 or more months after cessation are positively associated with the total number of person-to-person encounters (both individual and group): 12.4% for 0–1 contact, 16.3% for 2–3 contacts, 20.9% for 4–8 contacts, and 24.7% for more than 8 contacts.³¹ A dose–relationship has also been seen for length of contact.³¹

Counseling Interventions for Quitting

In providing counseling for quitting smoking, the goal is to facilitate the process of change by helping to ready the patient for permanent cessation. It is important to convey the view of quitting as a learning process that might take months or even years to achieve, rather than as a now-or-never event.

Counseling Patients Who Are Not Ready to Quit: Ongoing

Assessment

In counseling patients who are not ready to quit, an important first step is to encourage the patient to start thinking about quitting and to consider making a commitment to quit sometime in the foreseeable future. Sometimes patients who are not ready truly do not understand the need to quit. In general, most smokers will recognize the need to quit but are not yet ready to make the commitment to quit. Many patients will have tried to quit multiple times and relapsed; thus, they might feel too discouraged to try again.

Strategies for working with patients who are not ready to quit include increasing patient awareness of the available treatment options, having patients identify their reasons for smoking and for wanting to quit, and identifying barriers to quitting. Providers can also engage patients in thinking about quitting by raising awareness of specific drug interactions between medications and tobacco smoke ([Table 47–2](#)) and how tobacco use can induce or exacerbate medical conditions (e.g., chronic obstructive pulmonary disease, heart disease). Providers should also discuss the importance of preventive health, such as the recommendation for all adult smokers, 19–64 years of age to receive the pneumococcal vaccine to aid in the prevention of invasive pneumococcal disease.³⁴

Although it may be useful to provide patients with information about the medications available for quitting, it is not appropriate to recommend a treatment regimen until the patient is ready to quit in the near future (e.g., within the next month). A treatment goal at this stage should be to promote motivation to quit. Providers can encourage patients to seriously consider quitting by asking the following series of three questions:

1. “Do you ever plan to quit?”

If the patient responds “no,” the provider should inquire, “What would have to change for you to decide to quit?” If the patient indicates that nothing would change his or her opinion about quitting, then the provider should offer to assist if or when the patient changes his or her mind. If the patient responds “yes,” the provider should continue to question 2.

2. “How would it benefit you to quit now, instead of later?”

Quitting generally becomes more difficult the longer a patient smokes. Most patients will agree that there is never an ideal time to quit, and that postponing quitting has more negative effects than positive.

3. “What would have to change for you to decide to quit sooner?”

This question probes patients’ perceptions about quitting and can reveal specific barriers to quitting that can be discussed and addressed.

Counseling Patients Who Are Ready to Quit

The goal for patients who are ready to quit in the next month is to achieve cessation by providing an individualized treatment plan that addresses the key issues listed in [Table 47–3](#). The first step is to discuss the patient’s tobacco use history by inquiring about levels of smoking (cigarettes/day), number of years smoked, methods used previously for quitting (if any), and reasons for previous failed quit attempts. Providers should fully understand the basis for personal preferences for the different pharmacotherapies for quitting and then work with each patient in selecting the quitting methods (e.g., medications or behavioral counseling programs). It is important to recognize that pharmacotherapy might not be desirable or affordable for all patients. However, providers should educate patients that medications, when taken correctly, can substantially increase the likelihood of quitting successfully,³¹ and that the costs of continuing smoking far outweigh the costs of the medications.

TABLE 47–3 Key Topics for Individualized Tobacco Cessation Plans

Topic	Description
Assess tobacco use history	• Current use: – Type(s) and amount of tobacco used • Past use: – Duration of smoking – Recent changes in levels of use • Past quit attempts: – Number of attempts, date of most recent attempt, duration of abstinence – Previous methods: What did or did not work? Why or why not?

Topic	Description
	- Previous experience with cessation pharmacotherapy: agent used, adequacy of dose, adherence, duration of treatment - Reasons for relapse • Reasons or motivation for wanting to quit (or stay quit) • Confidence in ability to quit (or stay quit) • Triggers for smoking • Routines and situations associated with smoking • Stress-related smoking • Social support for quitting • Concerns about weight gain • Concerns about withdrawal symptoms
Facilitate the quitting process	• Discuss methods for quitting: pros and cons of the different methods • Set a quit date, ideally within the next 2 weeks • Discuss coping strategies • Discuss withdrawal symptoms • Discuss concept of a slip (occasional smoking) versus full relapse • Provide medication counseling: adherence and proper use • Offer to assist throughout the quit attempt
Arrange and provide follow-up counseling	• Monitor the patient's progress throughout the quit attempt • Evaluate the current quit attempt - Status of attempt - Slips (occasional smoking) and relapses - Medication use: ▪ Adherence with regimen ▪ Plans for discontinuation - Address temptations and triggers; discuss relapse prevention strategies - Provide encouragement throughout the quit attempt • Follow-up contacts (face-to-face, by telephone, or by e-mail): first contact during first week after quitting, second contact within the first month, additional contacts scheduled as needed

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Ideally, patients will select a quit date that is within the next 2 weeks, allowing ample time to prepare themselves and their environment before the actual quit date. This preparation includes removing all tobacco products and ashtrays from the home, car, and workplace. Patients should be advised to discuss their desire to quit with their family, friends, and coworkers and to request their support and assistance. Having patients think about when and why they smoke can help them anticipate situations that might trigger a desire to smoke and contribute to relapse. Additional counseling strategies to address with patients during a quit attempt are listed in [Table 47–4](#). Patients should be counseled on proper medication use (including administration), adverse effects, and adherence, and it is crucial to emphasize the importance of receiving behavioral counseling throughout the quit attempt. Additionally, patients should be advised to adhere to the entire course of pharmacotherapy, even though most withdrawal symptoms subside within 2–4 weeks.²¹

TABLE 47–4 Cognitive and Behavioral Strategies for Smoking Cessation

Cognitive Strategies	
Cognitive strategies focus on retraining of the way a patient thinks. Often, patients mentally deliberate on the fact that they are thinking about a cigarette, and this leads to relapse. Patients must recognize that thinking about a cigarette does not mean they need to have one.	
Review commitment to quit	Each morning say, “I am proud that I made it through another day without tobacco!” Remind oneself that cravings and temptations are temporary and will pass. Announce, either silently or aloud, “I am a nonsmoker, and the temptation will pass.”
Distractive thinking	Practice deliberate, immediate refocusing of thinking toward other thoughts when cued by thoughts about tobacco use.
Positive self-talk, pep talks	Say: “I can do this,” and remind oneself of previous difficult situations in which tobacco use was avoided.
Relaxation through imagery	Center mind toward positive, relaxing thoughts.
Mental rehearsal, visualization	Prepare for situations that might arise by envisioning how best to handle them. For example, envision what would happen if offered a cigarette by a friend, mentally craft and rehearse a response, and perhaps even practice it by saying it aloud.

Behavioral Strategies

Behavioral strategies involve specific actions to reduce the risk for relapse. These strategies should be considered prior to quitting, after determining patient-specific triggers and routines or situations associated with tobacco use. Below are strategies for several of the more common cues or causes for relapse.

Stress	Anticipate upcoming challenges at work, at school, or in personal life. Develop a substitute plan for tobacco use during times of stress (e.g., use deep breathing, take a break or leave the situation, call a supportive friend or family member, use nicotine replacement therapy).
Alcohol	Drinking alcohol can lead to relapse. Consider limiting or abstaining from alcohol during the early stages of quitting.
Other smokers	Quitting is more difficult when other tobacco users are around. This is especially difficult if another tobacco user is in the household. During the early stages of quitting, limit prolonged contact with people who are using tobacco. Ask co-workers, friends, and housemates not to smoke or use tobacco in your presence.
Oral gratification needs	Have nontobacco oral substitutes (e.g., gum, sugarless candy, straws, toothpicks, lip balm, toothbrush, nicotine replacement therapy, bottled water) readily available.
Automatic smoking routines	Anticipate routines that are associated with tobacco use and develop an alternative plan. Examples: • Morning coffee: Change morning routine; drink tea instead of coffee; take shower before drinking coffee; take a brisk walk shortly after awakening. • While driving: Remove all tobacco from car; have car interior detailed; listen to an audiobook or talk radio; use oral substitutes. • While on the phone: Stand while talking; limit call duration; change phone location; keep hands occupied by doodling or sketching. • After meals: Get up and immediately do dishes or take a brisk walk after eating; call supportive friend.
Postcessation weight gain	In general, attempting to modify multiple behaviors at one time is not recommended. If weight gain is a barrier to quitting, engage in regular physical activity and adhere to a healthy diet (as opposed to strict dieting). Carefully plan and prepare meals; increase fruit, vegetable, and water intake to create a feeling of fullness; and chew sugarless gum or eat sugarless candy. Consider use of pharmacotherapy shown to delay weight gain (e.g., 4 mg nicotine gum, 4 mg nicotine lozenge, bupropion).
Cravings for tobacco	Cravings for tobacco are temporary and usually pass within 5–10 minutes. Handle cravings through distractive thinking, take a break, do something else, take deep

breaths.

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Counseling Patients Who Recently Quit

Patients who recently quit will face frequent, difficult challenges in countering withdrawal symptoms and cravings or temptations to use tobacco. An important step is to help them identify situations that might trigger relapse and to suggest appropriate coping strategies. Because smoking also is a habitual behavior, patients should be advised to alter daily routines that were previously associated with tobacco use. These changes will help to disassociate the behaviors from the tobacco.

Many people who quit using tobacco will experience cravings for years and even decades after quitting. Thus, counseling for relapse prevention should be part of every follow-up contact with patients who have recently or ever quit smoking. Patients who slip and smoke a cigarette (or use any form of tobacco) or experience a full relapse back to smoking should be encouraged to think through the scenario in which smoking first recurred and identify the trigger for relapse. Identifying triggers will provide valuable information for future quit attempts.

Counseling Patients Who Are Former Smokers

The strategies to be applied for former tobacco users are similar but typically less intensive than those to be applied for recent quitters. The goal for former tobacco users is to remain tobacco-free for life. Providers should evaluate the patient's resolve for staying tobacco-free and ongoing coping strategies; in this context, it is appropriate to ascertain whether the patient has had any strong temptations to use tobacco or has occasionally used any tobacco product. Also, it is important to ensure that patients are appropriately terminating or tapering pharmacotherapy products. Patients who have been tobacco-free should be congratulated for their success. For patients who have intermittently used tobacco, situations in which tobacco use occurred should be reviewed, and additional coping strategies should be discussed.

Helping Patients Quit: The Ask-Advise-Refer Approach (Brief Intervention)

Providers should familiarize themselves with local resources for tobacco cessation, including group programs and telephone quit lines. When time or lack of expertise limits the ability to provide comprehensive cessation counseling, providers are encouraged to apply an “abbreviated 5 A’s” model whereby they *ask* about tobacco use, *advise* tobacco users to quit, and *refer* patients to other resources for additional assistance, including local services, group counseling programs, and web-based applications. Community pharmacy personnel (pharmacists and technicians) can feasibly provide brief cessation interventions that include distributing quit line materials to patients interested in quitting.³⁵ Telephone-based counseling is available throughout the United States. These services provide low-cost interventions that can reach patients who might otherwise have limited access to medical treatment because of remoteness of geographic location or lack of financial resources. In clinical trials, telephone counseling services for which at least some of the contacts are initiated by the quit line counselor were shown to be effective in promoting abstinence.³¹ Compared with medication-alone therapy, combining medication with quit line counseling significantly improves abstinence rates.³¹ The national telephone number for the toll-free tobacco quit line is 1-800-QUIT-NOW.

Pharmacologic Therapy

Although in some situations pharmacotherapy should be used with caution or only under the supervision of a primary care provider (see later under Special Populations), most patients who are attempting to quit should be advised to incorporate pharmacotherapy in their treatment plan. Currently, seven first-line agents are approved by the U.S. Food and Drug Administration (FDA) for smoking cessation³¹: five formulations of nicotine replacement therapy (NRT), sustained-release bupropion, and varenicline. Three of the NRT formulations—gum, lozenge, and transdermal patch—are nonprescription, but the nicotine inhaler and nicotine nasal spray, as well as bupropion and varenicline, require a prescription.

Nicotine Replacement Therapy

NRT is the most commonly used pharmacotherapy for smoking cessation.³² NRT products often are used to help noncigarette tobacco users to quit, but these products are FDA labeled only to help cigarette smokers quit. Similar to the nicotine present in tobacco, the active agents in NRT stimulate the release of dopamine in the central nervous system.¹³ The rationale underlying the use of NRT for smoking cessation is twofold. First, NRT provides smokers with a nontobacco source of nicotine to reduce the physiologic symptoms of nicotine withdrawal that typically occur after abstinence from tobacco. Second, by attenuating the symptoms of withdrawal, NRT assists quitters by allowing them to focus on the behavioral and psychological aspects of smoking cessation. A key advantage of NRT is that patients, as well as those in the smoker's environment, are not exposed to the carcinogens and other toxic constituents present in tobacco and tobacco smoke. Because NRT products are regulated by FDA, they contain the labeled amount of nicotine, whereas non-regulated forms of nicotine delivery systems (e.g. electronic cigarettes) may significantly vary from the labeled concentration and contain ingredients that lack sufficient safety testing. Compared with cigarettes, NRT formulations provide lower, slower, and less-variable plasma nicotine concentrations,¹⁸ thereby eliminating the almost immediate reinforcing effects of nicotine obtained through smoking.

Nicotine is well absorbed (Figure 47–3) from many sites, including the lungs, skin, and nasal and buccal (oral) mucosa. Nicotine absorption is pH-dependent, and lower systemic concentrations are achieved under acidic conditions. Nicotine also is well absorbed from the gastrointestinal tract (small intestine) but undergoes extensive first-pass hepatic metabolism, resulting in negligible systemic levels of nicotine.¹⁸

FIGURE 47–3 Plasma nicotine concentrations over time for various nicotine delivery systems. (Source: Reproduced with permission from Rx for Change: Clinician-Assisted Tobacco Cessation program. The Regents of the University of California. Copyright © 1999–2020.)

The main difference between the various NRT formulations is the site and rate of nicotine absorption (Figure 47–3). Compared with cigarettes, all of the NRT formulations deliver nicotine less rapidly and achieve lower serum nicotine

levels, thereby lowering the likelihood of developing physical dependence. Peak serum concentrations are achieved most rapidly with the nasal spray (11–18 minutes), followed by the gum, lozenge, and inhaler (30–60 minutes) and then by the transdermal patch (3–12 hours). In contrast, significantly higher peak nicotine levels are attained within 10 minutes of smoking a cigarette.¹⁸

Patients should begin NRT on their quit date and discontinue use of all forms of tobacco on initiation of the NRT regimen. Use of tobacco in combination with NRT may result in serum nicotine concentrations that are higher than those achieved from tobacco products alone, increasing the likelihood of nicotine-related adverse effects, including nausea, vomiting, hypersalivation, perspiring, abdominal pain, dizziness, weakness, and palpitations.

Nicotine Polacrilex Gum

Nicotine polacrilex gum is a resin complex of nicotine and polacrilin in a sugar-free (<3 calories/piece) chewing gum base. The product is available as 2 mg and 4 mg strengths, in original (tobacco-like, peppery), cinnamon, fruit, and mint flavors (Table 47–5). All gum formulations contain buffering agents (sodium carbonate and sodium bicarbonate) to increase salivary pH, thereby enhancing absorption of nicotine across the buccal mucosa. When the 2 mg and 4 mg gums are used properly, approximately 1.6 mg and 2.2 mg of nicotine is absorbed from each dose, respectively. Peak serum concentrations of nicotine are achieved approximately 30 minutes after chewing a single piece of gum and then slowly decline over 2–3 hours.¹⁸

TABLE 47–5 Dosages for Nonprescription Nicotine Polacrilex Gum and Lozenge		
	Gum	Lozenge
Product strength	Nicorette: 2 mg, 4 mg; original, cinnamon, fruit, mint Generic: 2 mg, 4 mg; original, fruit, mint	Nicorette (standard): 2 mg, 4 mg; mint Nicorette (mini): 2 mg, 4 mg; mint Generic (standard): 2 mg, 4 mg; mint, cherry
Dose	First cigarette ≤30 minutes after waking: 4 mg First cigarette >30 minutes after waking: 2 mg Weeks 1–6: 1 piece every 1–2 hours Weeks 7–9: 1 piece every 2–4 hours	First cigarette ≤30 minutes after waking: 4 mg First cigarette >30 minutes after waking: 2 mg Weeks 1–6: 1 lozenge every 1–2 hours Weeks 7–9: 1 lozenge every 2–4 hours

	Gum	Lozenge
	<i>Weeks 10–12: 1 piece every 4–8 hours</i>	<i>Weeks 10–12: 1 lozenge every 4–8 hours</i>

The recommended dosage of nicotine gum is based on the “time to first cigarette” (TTFC) of the day. Having a strong desire or need to smoke soon after waking is viewed as a key indicator of nicotine dependence. Therefore, patients who smoke their first cigarette of the day within 30 minutes of waking are likely to be more highly dependent on nicotine and require higher dosages than those who delay smoking for more than 30 minutes after waking. Specifically, if the TTFC is 30 minutes or less, therapy should be initiated with the 4 mg gum. If the TTFC is more than 30 minutes, therapy should be initiated with the 2 mg gum. [Table 47–5](#) provides the manufacturer’s recommended dosing schedule. During the initial 6 weeks of therapy, patients should use 1 piece of gum every 1–2 hours while awake. In general, this amounts to at least 9 pieces of gum daily, which improves the overall chances of quitting. [Table 47–6](#) provides specific instructions for proper use of the nicotine gum. The “chew and park” method described in the table allows for the slow, consistent release of nicotine from the polacrillin resin. Patients can use additional pieces of gum (up to the maximum of 24 pieces per day) if cravings occur between the scheduled doses. In general, individuals who smoke heavily will need more pieces to alleviate their cravings.

TABLE 47–6 Usage Guidelines for Nicotine Polacrilex Gum

- Begin NRT on quit date and discontinue all forms of tobacco upon initiation of NRT regimen.
- Note that nicotine gum is a nicotine delivery system, not a chewing gum.
- Proper administration technique is necessary when using this product. Nicotine from the gum is released using the “chew and park” method:
 - Chew each piece of gum *slowly* several times.
 - Stop chewing at the first sign of a peppery, minty, fruity, or citrus taste, or after experiencing a slight tingling sensation in the mouth. This usually occurs after approximately 15 chews, but the time to effect onset varies.
 - Park the gum between the cheek and gum to allow absorption of nicotine across the lining of the mouth.
 - When the taste or tingling dissipates (generally after 1–2 minutes), slowly resume chewing.

- When the taste or tingle returns, stop chewing and park the gum in a different place in the mouth. This will decrease the incidence of mouth irritation.
- The chew and park steps should be repeated until most of the nicotine is gone, which is when the taste or tingle does not return after continued chewing. On average, each piece of gum lasts 30 minutes.

- To minimize withdrawal symptoms, use the nicotine gum on a scheduled basis rather than as needed.
- Follow the dosage regimen carefully; reduce the dosage at the recommended intervals; if needed for longer than 12 weeks of treatment to keep from smoking, talk to your HCP.
- Do not chew more than 24 pieces per day.
- Acidic beverages such as coffee, juices, wine, or soft drinks may transiently reduce the salivary pH, resulting in decreased absorption of nicotine across the buccal mucosa. Do not eat or drink anything (except water) 15 minutes before or while using the nicotine gum.
- Note that chewing the gum too quickly will result in an unpleasant taste caused by too much nicotine in the saliva, and that if the nicotine is swallowed, it may cause effects similar to those produced by excessive smoking (e.g., nausea, throat irritation, light-headedness, hiccups).
- Have nicotine gum readily available at all times. Keep the nicotine gum in the same place you previously kept your cigarettes (e.g., shirt pocket, purse, desk).
- Keep this product, including used pieces, out of the reach of children and pets.

Key: HCP = Health care provider; NRT = nicotine replacement therapy.

An important point to note is that patients often do not use enough of the gum to derive its full benefit or they use it incorrectly (e.g., incorrect chewing technique or concurrent consumption of beverages or foods that alter the pH of the mouth). An adherence screening question could be “Are you able to use this medicine nine or more times a day?” Commonly, patients chew too few pieces per day or shorten the duration of treatment. For this reason, recommending a fixed schedule of administration, tapering over 1–3 months, is preferable to having the patient use the gum as needed to control cravings.³¹

The most common adverse effects associated with the use of the nicotine gum include unpleasant taste, mouth irritation, jaw muscle soreness or fatigue, hypersalivation, hiccups, and dyspepsia. Many of these effects can be minimized or prevented by using proper chewing technique.³¹ The nicotine polacrillin resin is more viscous than ordinary chewing gum and more likely to adhere to fillings, bridges, dentures, crowns, and braces. Patients should be

warned that chewing the gum too rapidly may result in excessive release of nicotine, leading to lightheadedness, nausea, vomiting, irritation of the throat and mouth, hiccups, and indigestion.

Patients with active temporomandibular joint (TMJ) disease should not use the nicotine gum because the highly viscous consistency of the formulation and the need for frequent chewing may exacerbate the jaw condition. In addition, the manufacturer recommends that patients with sodium-restricted diet, stomach ulcers, or diabetes contact their primary care provider before use of the product because these more serious conditions may potentially necessitate further monitoring.

Nicotine Polacrilex Lozenge

The nicotine polacrilex lozenge is a resin complex of nicotine and polacrillin in a sugar-free mint- or cherry-flavored lozenge ([Table 47–5](#)). The lozenges are available in 2 mg and 4 mg strengths with two different physical sizes (regular and mini); they should be used similarly to other medicinal lozenges or troches (i.e., suck and rotate it within the mouth until it dissolves). Because the mini-lozenge is smaller, it is more easily concealed and dissolves more quickly. The pharmacokinetics of the nicotine lozenge and gum formulations are comparable, but a nicotine lozenge delivers approximately 25% more nicotine than an equivalent dose of nicotine gum because of complete dissolution of the dosage form.³⁶ The lozenge form also contains buffering agents (sodium carbonate and potassium bicarbonate) to increase salivary pH, enhancing the buccal absorption of nicotine.

As with nicotine gum, dosing for the lozenge is based on the TTFC. If the TTFC is 30 minutes or less, therapy should be initiated with the 4 mg lozenge. For a TTFC of more than 30 minutes, therapy should be initiated with the 2 mg lozenge. During the initial 6 weeks of therapy, patients should use 1 lozenge every 1–2 hours while awake. In general, this amounts to at least 9 lozenges daily. An adherence screening question could be “Are you able to use this medicine nine or more times a day?” [Table 47–7](#) provides further instructions for proper use of the nicotine lozenge. Patients can use additional lozenges (up to 5 lozenges in 6 hours or a maximum of 20 lozenges per day) if cravings occur between the scheduled doses. The manufacturer recommends that patients with sodium-restricted diets, stomach ulcers, or diabetes contact their primary care provider before using the lozenges because these more serious

conditions may necessitate further monitoring.

TABLE 47-7 Usage Guidelines for Nicotine Polacrilex Lozenge

- Begin NRT on quit date and discontinue use of all forms of tobacco on initiation of NRT regimen.
- Proper administration technique is necessary when using the nicotine lozenge:
 - Place the lozenge in the mouth and allow it to dissolve slowly (20–30 minutes for standard lozenge; 10 minutes for mini-lozenge). As the nicotine is released from the lozenge, you may experience a warm, tingling sensation.
 - To reduce the risk of side effects (e.g., nausea, hiccups, and heartburn), do not chew or swallow the lozenge.
 - Occasionally rotate the lozenge to different areas of the mouth to decrease mouth irritation.
- To minimize withdrawal symptoms, use the nicotine lozenge on a scheduled basis rather than as needed.
- Follow the dosage regimen carefully; reduce the dosage at the recommended intervals; if needed for longer than 12 weeks of treatment to keep from smoking, talk to your HCP.
- Do not use more than 5 lozenges in 6 hours or more than 20 lozenges per day.
- Acidic beverages such as coffee, juices, wine, or soft drinks may transiently reduce the salivary pH, resulting in decreased absorption of nicotine across the buccal mucosa. Do not eat or drink anything (except water) 15 minutes before or while using the nicotine lozenge.
- Patients who use more than 1 lozenge at a time, continuously use 1 lozenge after another, or chew or swallow the lozenge are more likely to experience heartburn or indigestion.
- Have nicotine lozenges readily available at all times. Keep the nicotine lozenges in the same place you previously kept your cigarettes (e.g., shirt pocket, purse, desk).
- Keep this product out of the reach of children and pets.

Key: HCP = Health care provider; NRT = nicotine replacement therapy.

Adverse effects associated with the nicotine lozenge include mouth irritation, nausea, hiccups, cough, heartburn, headache, flatulence, and insomnia. Patients who use more than 1 lozenge at a time, continuously use 1 lozenge after another, or chew or swallow the lozenge are more likely to experience heartburn or indigestion.

Nicotine Transdermal Systems (Nicotine Patch)

Nicotine transdermal systems deliver continuous, low levels of nicotine

through the skin over 24 hours. The patch consists of a waterproof surface layer, a nicotine reservoir, an adhesive layer, and a disposable protective liner.

The dosing schedules for the nicotine patches vary slightly ([Table 47–8](#)). Before recommending a specific product and a dosing schedule, the provider should know how many cigarettes the patient smokes per day. In general, heavier smokers will require higher-strength formulations for a longer duration of therapy. Patients who experience adverse effects such as dizziness, perspiration, nausea, vomiting, diarrhea, or headache should consider a lower-strength patch. Additional instructions for proper use of the nicotine patch are listed in [Table 47–9](#).

TABLE 47–8 Dosages for Nonprescription Nicotine Transdermal Systems (Patch)

Dosage Feature	NicoDerm CQ and Generic Patch
Product strength	7, 14, 21 mg (24 hour)
Dose	<i>>10 cigarettes/day</i> 21 mg/day × 4–6 weeks 14 mg/day × 2 weeks 7 mg/day × 2 weeks <i>≤10 cigarettes/day</i> 14 mg/day × 6 weeks 7 mg/day × 2 weeks

TABLE 47–9 Usage Guidelines for Nicotine Transdermal Systems (Nicotine Patch)

- Begin NRT on quit date and discontinue use of all forms of tobacco on initiation of NRT regimen.
- Apply the patch to a clean, dry, hairless area of the skin on the upper body or the upper outer part of the arm at approximately the same time each day. An electric razor can be used to create a hairless application site.
- The patch should be applied to a different area of skin each day. Avoid areas with new and healing tattoos. To minimize the potential for local skin reactions, the same area should not be used again for at least 1 week.
- During application, apply firm pressure to the patch with the palm of the hand for 10 seconds. Be sure that the patch adheres well to the skin, especially around the edges; this is necessary for a good seal.
- Wash your hands after applying or removing the patch.
- The patch should not be left on the skin for more than 24 hours because prolonged use may lead to skin irritation.
- Any adhesive remaining on the skin after patch removal can be removed with rubbing

alcohol.

- Water will not reduce the effectiveness of the nicotine patch if it is applied correctly. You may bathe, swim, shower, or exercise while wearing the patch.
- Do not cut patches in half or into smaller pieces to adjust or reduce the nicotine dosage. Nicotine in the patch may evaporate from the cut edges and the patch may be less effective.
- Local skin reactions (e.g., itching, burning, redness) are common with the nicotine patch. These reactions are generally caused by adhesives; they can be minimized by rotating patch application sites and, if they occur, treated with nonprescription hydrocortisone cream.
- Remove the nicotine patch before having a magnetic resonance imaging (MRI) procedure. Burns from nicotine patches worn during MRI scanning have been reported and probably are caused by the metallic component in the backing of some patches.
- Users experiencing troublesome dreams or other sleep disruptions should remove the patch before bedtime.
- Discard the removed nicotine patch by folding it onto itself, completely covering the adhesive area.
- Keep new and used patches out of the reach of children and pets.

Key: NRT = Nicotine replacement therapy.

The most common adverse effects associated with the nicotine patch are local skin reactions (erythema, burning, and pruritus) at the application site, which generally are caused by skin occlusion or sensitivity to the patch adhesives. If the skin reaction is bothersome, the patient can apply nonprescription hydrocortisone cream to the site or try another manufacturer's product that uses a different adhesive. Other, less common adverse effects include vivid or abnormal dreams, insomnia, and headache. Sleep disturbances might be caused by nocturnal nicotine absorption. If this effect becomes troublesome, patients should be instructed to remove the patch at bedtime; of note, a new patch should be applied as soon as possible after waking the following morning because the lack of nicotine coverage throughout the night may lead to an increased urge to smoke.³¹ Additionally, a short-acting NRT could be used after waking to bridge therapy.

Prescription Medications for Smoking Cessation

Detailed information about prescription products for tobacco cessation is outside the scope of this discussion. The following information is a summary of

key information; for further details, the reader is encouraged to consult another reference that specializes in this content.

Nicotine Inhaler

The nicotine inhaler consists of a plastic mouthpiece and a menthol-flavored nicotine-containing cartridge that delivers 4 mg of nicotine as an inhaled vapor, 2 mg of which is absorbed across the oropharyngeal mucosa. The inhaler reduces nicotine withdrawal symptoms and may give some degree of comfort by providing a hand-to-mouth ritual that emulates the act of smoking. However, reinforcing the hand-to-mouth ritual can make quitting more difficult. A gradual reduction in inhaler use is recommended. The inhaler has not been evaluated for use in patients with bronchospastic diseases, such as asthma, so it should be used with caution in these patients because of the risk of exacerbation.³⁷ Adverse effects of the inhaler include mild mouth and throat irritation, cough, and rhinitis.

Nicotine Nasal Spray

The nicotine nasal spray is an aqueous solution of nicotine for administration to the nasal mucosa. Each actuation delivers a 0.5 mg bolus of nicotine that is absorbed across the nasal mucosa. Because of its rapid onset of action (relative to other NRT formulations), the spray is a potential option for patients who prefer a medication to manage withdrawal symptoms rapidly; however, in 15%–20% of patients, use of the nasal spray can result in dependence. The nasal spray is not recommended for patients with chronic nasal disorders. Some patients with asthma have reported bronchospasm after using the nasal spray, so use of this medication in patients with bronchospastic disease should be avoided.³⁷ Initially, most patients will experience nose and throat irritation (peppery sensation), watery eyes, sneezing, or coughing when using this product. This product is to be administered without sniffing (i.e., not administered using the same technique as for standard allergy nasal sprays). After the first week, most patients have minimal difficulty with the product, and tolerance generally develops with regular use. A gradual reduction in nasal spray use is recommended.

Sustained-Release Bupropion

Sustained-release bupropion was the first non-nicotine medication approved for smoking cessation. This agent is a prescription antidepressant medication

that is believed to promote smoking cessation by blocking the reuptake of dopamine and norepinephrine in the brain, thereby decreasing the cravings for cigarettes and symptoms of nicotine withdrawal.³¹

Therapy is started with a dose of 150 mg orally every morning for 3 days, followed by 150 mg twice daily for 7–12 weeks. Because steady-state blood levels are reached after approximately 7 days of therapy, patients set their quit date for 1–2 weeks after starting therapy. Insomnia and dry mouth are the most common adverse effects reported with bupropion. Because seizures have been reported in approximately 0.1% of patients, bupropion is contraindicated in patients who (1) have a seizure disorder, (2) have a current or previous diagnosis of anorexia or bulimia nervosa, (3) are undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines), (4) are currently using or have used a monoamine oxidase inhibitor within the past 14 days, or (5) are currently being treated with any other medications that contain bupropion. Other factors that may potentially increase the odds of seizure and are classified as warnings for use of this medication include history of head trauma or previous seizure, central nervous system tumor, severe hepatic cirrhosis, and concomitant use of medications that lower the seizure threshold. A black-box warning that highlighted risks of serious neuropsychiatric symptoms was removed from product labeling in 2016.³⁸ This labeling change was made when results of a large trial of smokers with comorbid psychiatric disorders suggested that bupropion and varenicline have no higher risk of associated adverse psychiatric events than NRT.³⁹ Pharmacotherapy should ideally be coordinated with the patient's behavioral health team to promote appropriate monitoring. Although reports are rare, FDA still recommends that providers and patients monitor for changes in mood and behavior during treatment with bupropion.³⁸

Varenicline

Varenicline (Chantix) is a partial agonist and is highly selective for the alpha-4 beta-2 nicotinic receptor. The efficacy of varenicline in smoking cessation is believed to be the result of sustained, low-level agonist activity at the receptor site that is combined with competitive inhibition of nicotine binding. The partial agonist activity induces modest receptor stimulation, leading to increased dopamine levels that attenuate the symptoms of nicotine withdrawal. In addition, by competitively blocking the binding of nicotine to nicotinic acetylcholine receptors in the central nervous system, varenicline

inhibits the surges of dopamine release that occur immediately after inhalation of tobacco smoke. The latter mechanism may be effective in preventing relapse by reducing the pleasure associated with smoking.⁴⁰

As with sustained-release bupropion, treatment with varenicline should be started 1 week before the patient stops smoking. This regimen allows for gradual escalation of the dose to minimize treatment-related nausea and insomnia. Therapy is generally started at 0.5 mg daily on days 1–3; 0.5 mg twice daily on days 4–7; and 1 mg twice daily for weeks 2–12. For patients who are not able to quit abruptly, an approved regimen suggests that they begin varenicline dosing and reduce smoking by 50% within the first 4 weeks, then by an additional 50% in the next 4 weeks, and continue reducing with the goal of complete abstinence by 12 weeks; they may continue treatment an additional 12 weeks for a total of 24 weeks.⁴¹ Nausea, insomnia, abnormal dreams, and headache are the most commonly reported adverse effects. Some people have experienced increased drunkenness (intoxication), unusual or sometimes aggressive behavior, and/or having no memory of things that have happened while drinking alcohol and using this medication.⁴² Similarly to bupropion, a black-box warning that highlighted risks of serious neuropsychiatric symptoms was removed from product labeling in 2016. This labeling change was made when results of the EAGLES trial of smokers with comorbid psychiatric disorders suggested that bupropion and varenicline have no higher risk of associated adverse psychiatric events than NRT.³⁹ Pharmacotherapy should ideally be coordinated with the patient's behavioral health team to promote appropriate monitoring. Although reports are rare, the FDA still recommends that providers and patients monitor for changes in mood and behavior during treatment with varenicline.⁴³

A small increased risk of cardiac events has been reported in some patients with existing cardiovascular disease.⁴⁴ In 2012, FDA shared results of a meta-analysis conducted by the manufacturer of varenicline, reporting that a higher occurrence of major adverse cardiovascular events was observed in patients using varenicline than in persons taking a placebo (although the increased risk was not statistically significant).^{45,46} The warnings and precautions labeling was updated to include the results of the meta-analysis and included instructions to patients to notify their health care providers of new or worsening cardiovascular symptoms and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke. The labeling also suggests that the known benefits of varenicline for smoking

cessation should be weighed against the potential harms in patients with cardiovascular disease.⁴¹

Pharmacotherapeutic Comparison

Few trials have directly compared the various agents for smoking cessation. In general, compared with placebo, regimens with the first-line agents approximately double the long-term quit rates^{31,47} (Table 47–10). An open-label comparison of varenicline, nicotine patch, and combination therapy produced no significant differences in abstinence rates at 26 weeks for motivated adults.⁴²

TABLE 47–10 Methods for Smoking Cessation: Estimates of Treatment Efficacy for First-Line Agents Compared With Placebo at 6 Months After Quitting

Pharmacotherapy	Estimated Odds Ratio ^a (95% CI)	Estimated Abstinence Rate ^b (95% CI)
Placebo	1.0	13.8
Monotherapy (first-line agents)		
Sustained-release bupropion	2.0 (1.8–2.2)	24.2 (22.2–26.4)
Nicotine gum (6–14 weeks)	1.5 (1.2–1.7)	19.0 (16.5–21.9)
Nicotine inhaler	2.1 (1.5–2.9)	24.8 (19.1–31.6)
Nicotine lozenge (2 mg)	2.0 (1.4–2.8)	24.2 ^c
Nicotine patch (6–14 weeks)	1.9 (1.7–2.2)	23.4 (21.3–25.8)
Nicotine nasal spray	2.3 (1.7–3.0)	26.7 (21.5–32.7)
Varenicline (2 mg/day)	3.1 (2.5–3.8)	33.2 (28.9–37.8)
Combination Therapy (first-line agents)		
Nicotine patch (>14 weeks) + as-needed NRT (gum, nasal spray, or lozenge ^d)	3.6 (2.5–5.2)	36.5 (28.6–45.3)
Nicotine patch + bupropion SR	2.5 (1.9–3.4)	28.9 (23.5–35.1)
Nicotine patch + nicotine inhaler	2.2 (1.3–3.6)	25.8 (17.4–36.5)

^a Estimated relative to placebo.

^b Abstinence percentages for specified treatment.

^c One qualifying randomized trial; 95% CI not reported in the 2008 clinical practice guideline.

^d A recent trial, not included in the clinical practice guideline, supports the combination of the nicotine patch and nicotine lozenge.⁴²

Key: CI = Confidence interval; NRT = nicotine replacement therapy; SR = sustained release.

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Product Selection Guidelines

Because all first-line, FDA-approved cessation medications enhance quit rates, the choice of therapy is based largely on contraindications or precautions, patient preference, tolerability of the available dosage forms, use during previous quit attempts (i.e., what worked well and what did not, regardless of whether or not the medication was being used correctly), and cost. For whatever regimen selected, the cost of treatment will be insignificant compared with the costs of continued smoking and the costs of managing the resultant complications.

The number of smokeless tobacco products available on the market, including dissolvable tobacco and electronic cigarettes, is on the rise. Currently no guidelines exist for the treatment of tobacco cessation for people using these products. A review and meta-analysis supports the use of varenicline for smokeless tobacco users, although product labeling has not been changed.⁴³

Since 2016, FDA has increased its regulatory oversight of all tobacco products, including cigars, electronic cigarettes, and hookah and pipe tobacco. On December 20, 2019, the President signed legislation raising the federal minimum age to purchase tobacco products from 18 to 21 years of age.⁴⁸ In January 2020, FDA issued a policy that restricts any flavored pod or cartridge-based ENDS product other than menthol or tobacco-flavors. Of note, this

restriction does not include e-liquids sold in vape shops; however, these operations may be considered manufacturers.⁴⁸ Finally, manufacturers now have to comply with all FDA requirements, including reporting all ingredients and listing health warnings on packaging and advertising.

Special Populations

NRT should be used with caution in patients with serious underlying cardiovascular disease, including those who have had a recent myocardial infarction (i.e., within the preceding 2 weeks), those with serious arrhythmias, and those with serious or worsening angina pectoris.³¹ Nicotine may increase the myocardial workload by increasing the heart rate and blood pressure and also may constrict coronary arteries, leading to cardiac ischemia.⁴³ Although most experts believe that the risks of NRT in patients with cardiovascular disease are small relative to the risks of continued smoking,^{49,50} patients with serious underlying cardiovascular disease are advised to use NRT only while under the supervision of a health care provider.

Evidence exists for risk to the human fetus when prescription formulations of nicotine are used during pregnancy.⁵¹ (See the Preface for a detailed explanation of the pregnancy data.) Although NRT may pose a risk to the developing fetus, some experts have argued that NRT use during pregnancy is safer than continued smoking.^{51,52} However, because data showing effectiveness of NRT in pregnancy are inconclusive and because nicotine has the potential to cause fetal harm, the 2008 clinical practice guideline states that pregnant women should be encouraged to quit without the use of medication. Instead, providers are advised to offer interventions of person-to-person behavioral counseling for their pregnant patients who smoke.³¹

The efficacy of NRT, sustained-release bupropion, and varenicline has not been established in pediatric or adolescent smokers, and no NRT product is currently indicated for use in these populations.³¹ Accordingly, counseling is the recommended treatment method for smokers younger than 18 years.

People older than 65 years can benefit greatly from quitting smoking. Pharmacologic therapy and counseling are recommended. If mobility is an issue, referral to a quit line may be useful.^{16,31}

The manufacturers of nicotine gum, lozenge, and patch products recommend that patients taking a prescription medicine for asthma or depression speak

with their primary care provider before using nonprescription NRT. Fluvoxamine and theophylline (both now used infrequently) and inhaled corticosteroids have known clinically significant interactions with tobacco smoke ([Table 47–2](#)).

People who are lesbian, gay, bisexual, or transgender (LGBT) have more risk factors for cigarette use including increased second-hand smoke exposure and daily stressors due to perceived stigma.⁵³ In 2016, LGB adult cigarette use in the US was reported as higher than that of heterosexual/straight individuals (20.5% vs. 15.3%, respectively).⁵³

For light smokers (those who smoke fewer than 10 cigarettes per day and those who do not smoke every day), counseling is the recommended treatment method.³¹ However, the nicotine patch is approved for use in light smokers, and the nicotine lozenge was shown to be effective in individuals who smoke 15 or fewer cigarettes daily.⁵⁴ Use of smokeless tobacco (e.g., snuff, moist snuff, chewing tobacco, dissolvable tobacco), cigars, and pipes can produce nicotine addiction and lead to serious health consequences. Behavioral counseling is the recommended treatment method for these tobacco users.³¹

Patient Factors

When recommending a nonprescription agent for smoking cessation, primary care providers should determine the patient's smoking patterns, lifestyle habits, and coexisting medical conditions. In general, higher levels of smoking will require higher dosages of NRT and longer durations of treatment.

Some patients might need to use their smoking cessation medication longer than the usual recommended treatment duration. Although the general goal is complete—long-term abstinence from all nicotine-containing products—some smokers may benefit from long-term medication use.³¹ If continued use helps prevent relapse, this approach is considered preferable to the patient returning to smoking.³¹

Patients who smoke continuously throughout the day may have better success with a nicotine patch because it provides a sustained, steady release of nicotine. Conversely, patients who smoke intermittently throughout the day or who smoke intensely for short periods of time, followed by long periods of abstinence, might prefer a relatively short-acting formulation, such as a

nicotine gum or lozenge, to more closely mimic their tobacco use patterns. For some quitters, frequent gum chewing may not be feasible or socially acceptable. The nicotine patch, which can be concealed under clothing, might be a reasonable choice for these patients. Others may find nicotine lozenges, which can be used more discreetly, to be an acceptable alternative. Patients with underlying dermatologic conditions (e.g., psoriasis, eczema, atopic dermatitis) or allergy to adhesive tape are more likely to experience skin irritation and should not use the nicotine patch. The nicotine lozenge or patch is more appropriate than the nicotine gum for patients with TMJ disease or dentures. Finally, patients with serious cardiovascular disease, women who are pregnant or nursing, light smokers, and adolescents should be referred for further evaluation by their primary provider before starting treatment with NRT.

Patient Preferences

Identifying the patient's perceptions and expectations about pharmacotherapy, including the ability to adhere to the regimen, previous experience with smoking cessation medications, and concern about weight gain, is particularly important. Because NRT formulations require frequent dosing or nontraditional routes of administration, patient education about proper use of these products is essential. Patients who have difficulty taking multiple doses of medications throughout the day or those who want a simplified regimen might achieve greater success with the nicotine patch. By contrast, the gum or lozenge may be preferable for patients who want to titrate nicotine levels to manage withdrawal symptoms. Some people may find that they need an oral substitute for tobacco; the oral gratification given by the nicotine gum, lozenge, or inhaler might be beneficial in these patients. Others may prefer the idea of using a combination of medications, such as the nicotine patch plus gum or lozenge, on an as-needed basis, as discussed later in this section.

All smokers making a repeat quit attempt should be queried about their previous use of pharmacotherapy and their perceptions of available treatment options. For patients reporting a favorable past experience with a given product, repeated treatment with the same agent may be appropriate, with consideration given to increasing the dose, frequency of dosing, or duration of therapy. For patients who report a negative experience with a particular medication (e.g., poor adherence, adverse effects, palatability issues, cost), a

different regimen should be considered. For example, for a quitter who had short-term success with the patch but discontinued therapy because of intolerable nightmares, a second trial of the patch that is removed at bedtime is more likely to be successful. A patient who is unable to tolerate nicotine gum because of jaw muscle ache could be advised to switch to the nicotine lozenge or patch. For a patient who expresses concern about postcessation weight gain, use of the 4 mg nicotine gum or lozenge or sustained-release bupropion may be particularly helpful in that these products were shown to delay weight gain after quitting.³¹ Among patients for whom the out-of-pocket expense poses a potential barrier to pharmacologic treatment, use of the generic formulations is preferable.

Combination therapy should be considered a first-line treatment and might be particularly appropriate in patients who have experienced numerous failed attempts using monotherapy. Combination therapy generally involves the use of a long-acting medication (nicotine patch or sustained-release bupropion) in combination with a short-acting nicotine formulation (nicotine gum, lozenge, inhaler, or nasal spray). The long-acting nicotine formulation, which delivers relatively constant concentrations of drug, is used to prevent the onset of severe withdrawal symptoms, whereas the short-acting nicotine formulation, which delivers nicotine more rapidly, is used as needed to control withdrawal symptoms that may emerge during potential relapse situations (e.g., after meals, during episodes of stress, being around other smokers). Research suggests that combination therapy may be somewhat more efficacious than monotherapy.^{31,55} Disadvantages of combination therapy are the possibility of additional adverse effects (e.g., nicotine toxicity), difficulty with adherence, and increased cost. For other combination regimens, patients should be referred to their primary care provider to determine the most appropriate option.

Complementary Therapies

Although a variety of herbal and homeopathic products are available to aid cessation, data supporting their safety and efficacy are lacking. Many herbal preparations for cessation contain lobeline (derived from *Lobelia inflata*), an herbal alkaloid with partial nicotinic agonist properties. A meta-analysis⁵⁶ and a multicenter trial⁵⁷ found no evidence to support the role of lobeline as an aid for smoking cessation. Similarly, controlled trials did not find hypnosis or acupuncture to be an effective treatment for smoking cessation.^{31,58}

Electronic Cigarettes

Electronic cigarettes (e-cigarettes or ENDS) continue to gain popularity in the United States. These devices were initially marketed as a substitute for cigarettes in situations that do not allow smoking; however, many places have now also banned their use. Although found to be less harmful than regular cigarettes, e-cigarettes produce a breathable aerosol that still contains the highly addictive substance nicotine as well as other harmful chemicals and carcinogens, such as nitrosamines and diethylene glycol.⁵⁹ Specific to a potentially serious side effect, seizures may be associated with e-cigarette use.⁶⁰ Although compelling, data remain insufficient to support the safety or efficacy of these products in reducing or stopping smoking.⁶¹ The ACC consensus review offers suggestions on how to use e-cigarettes for those motivated to quit smoking.⁶² In a multicenter randomized study, e-cigarettes were found to increase smoking abstinence rates compared with traditional nicotine replacement therapy (NRT) (1 year abstinence rates: 18% and 9.9%, respectively).⁶³

E-cigarettes or vaporizers come in a variety of shapes and flavors, making them more marketable to children and young adults. For example, some products are pod- or cartridge-based and shaped like USB drives, making them easier to conceal, and were marketed in flavors like chocolate, mint, and multiple fruity flavors, to name just a few. The January 2020 restrictions on sale of those flavors is being enforced. E-cigarettes are the most commonly used tobacco product among youth, and youth are more likely than an adult to use an e-cigarette.⁵⁹ In April 2018, FDA introduced the Youth Tobacco Prevention Plan, an initiative that is focused on stopping youth use of tobacco products, and in particular, e-cigarettes. It includes a series of enforcement and regulatory steps as well as an educational campaign.⁶⁴ As this field continues to rapidly evolve, parents, teachers, and health care workers can help to prevent and reduce young people's use of e-cigarettes by staying updated on current trends and learning about what products are available, the harmful and potentially harmful ingredients, and the many emerging health risks.

Algorithm: Tobacco Cessation

FIGURE 47–2 Self-care for tobacco cessation. Key: 5 A's = Ask, advise, assess,

assist, arrange; MI = myocardial infarction; NRT = nicotine replacement therapy; OTC = over-the-counter; PUD = peptic ulcer disease; Rx = prescription; TMJ = temporomandibular joint.

Assessment of Tobacco Cessation: A Case-Based Approach

To help patients succeed at tobacco cessation, the provider must assist them in evaluating their patterns of smoking, identify medications and quitting methods they have or have not tried in the past, and determine appropriate cessation therapies. Analysis of smoking patterns and triggers for smoking will help the provider work with the patient to develop an appropriate treatment plan.

Cases 47–1 and 47–2 illustrate the assessment of two patients in different phases of quitting smoking.

Case 47–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient would like information about the various nonprescription medications for tobacco cessation. He is noticing that he gets more "winded" when he walks, and he is concerned about the effects of smoking on his health. He has smoked one pack per day (or 20 cigarettes) for 21 years. He smokes 2 cigarettes with his morning coffee and smokes in social situations such as when having a few drinks with coworkers. He has not received cessation counseling from a provider. He has tried the nicotine patch and gum in the past

Relevant Evaluation Criteria	Scenario/Model Outcome
	and wants to try Chantix (varenicline).
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	He is in a rush because he has to get back to work. He smokes mostly on work breaks and at home in the morning and in the evenings after dinner.
c. Description of the patient's efforts to relieve the symptoms	He has tried to quit smoking approximately 5 times to date, 3 times using NRT.
d. Patient's identity	Kevin Stills
e. Patient's age, gender, height, and weight	61 years old, male, 5 ft 8 in., 170 lb
f. Patient's occupation	Accountant
g. Patient's dietary habits	Reasonably healthy diet; walks 30 minutes daily during his lunch break.
h. Patient's sleep habits	Sleeps 7 hours/night during the workweek; does not have trouble sleeping.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Hypertension: controlled on lisinopril 10 mg daily
j. Allergies	NKA
k. History of other adverse reactions to medications	None
l. Other (describe)	Mr. Stills is married, with no children. His wife is supportive of his attempt to quit. Some close friends and coworkers also smoke.

Relevant Evaluation Criteria	Scenario/Model Outcome
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Patient is a middle-aged man who would like to quit smoking to improve his breathing and overall health.
3. Identify exclusions for self-treatment (Figure 47-2).	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Recommend pharmacotherapy and counseling. Pharmacotherapy options include • Nicotine patch • Nicotine gum • Nicotine lozenge • Combination therapy with the nicotine patch plus a short-acting NRT formulation • Referral to PCP for prescription pharmacotherapy (nicotine inhaler, nicotine nasal spray, bupropion SR, varenicline) (2) Refer Mr. Stills to telephone counseling (1-800-QUIT-NOW) or text-based services and applications because he is in a hurry. (3) Recommend that he set a quit date in 1-2 weeks. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account	Mr. Stills expressed interest in taking varenicline. Refer him to his PCP for a prescription.

Relevant Evaluation Criteria	Scenario/Model Outcome
patient preferences.	
	For behavioral counseling, refer him to the quit line. (See Tables 47-3 and 47-4.)
6. Describe the recommended therapeutic approach to the patient or caregiver.	“Medication is recommended. Although you have no contraindications or precautions for medication use as part of a self-care quit program, varenicline is available only by prescription.”
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	“Use of Chantix, or varenicline, is considered a first-line treatment for smoking cessation. Because you would like to take this medication and it is available by prescription only, you will need to contact your PCP to obtain a prescription. I can also call your provider for you now if you would like. Receiving counseling, in addition to taking Chantix as directed, will increase your chances of success with quitting.”
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	Criterion does not apply in this case.
Solicit follow-up questions from the patient or caregiver.	“What should I do if I am tempted to smoke when I am around my friends?”
Answer the patient's or caregiver's questions.	“The quit line counselor will be able to talk to you about problem-solving and coping skills for your smoking triggers. It is important that your friends and wife support you when you quit. To minimize relapse, reduce or avoid use of alcohol during the first 2 weeks of your quit attempt. The counselor will arrange follow-up contacts after your quit date.”

Relevant Evaluation Criteria	Scenario/Model Outcome
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Mr. Stills plans to contact his PCP and will return to the pharmacy to fill his prescription. He also set a quit date in 2 weeks with plans to follow up with the quit line.

Key: NKA = No known allergies; NRT = nicotine replacement therapy; PCP = primary care provider; SR = sustained release.

Case 47–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient quit smoking 7 days ago and is using the generic 21 mg nicotine patch. She complains of trouble sleeping and is experiencing disturbing dreams since starting to use the patch. She had been smoking approximately 1.5 packs per day (approximately 30 cigarettes daily) for 10 years before quitting.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Before quitting, patient used to have a cigarette before even getting out of bed because she had such intense cravings.

Relevant Evaluation Criteria	Scenario/Model Outcome
c. Description of the patient's efforts to relieve the symptoms	Patient has been using the 21 mg nicotine patch for 7 days. She had not previously tried pharmacotherapy for quitting. She purchased the patch after speaking to an HCP. She has not received any formal counseling from a provider. She feels a bit agitated and irritable from time to time during the day; she is very tempted to smoke in the morning when she wakes up. Overall, she likes the patch and is not experiencing any significant skin reactions.
d. Patient's identity	Kristen Brady
e. Patient's age, gender, height, and weight	28 years old, female, 5 ft 6 in., 140 lb
f. Patient's occupation	Web designer
g. Patient's dietary habits	Tries to "eat healthy"; drinks approximately 8 cups of caffeinated coffee per day.
h. Patient's sleep habits	Sleeps 7-8 hours a night. Since using the patch, she has experienced trouble sleeping and disturbing dreams.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Ms. Brady is not pregnant or lactating.
	She has TMJ disease, for which she takes acetaminophen 325 mg every 6 hours as needed for pain, but she rarely takes it.
j. Allergies	NKA
k. History of other adverse reactions to medications	None
l. Other (describe)	Patient is single. Her boyfriend and her roommate are supportive of her desire to quit.
Assess	

Relevant Evaluation Criteria	Scenario/Model Outcome
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Patient quit smoking 1 week ago and is experiencing "intolerable" adverse effects from the nicotine patch (i.e., sleep disturbances), daily withdrawal symptoms (i.e., agitation, irritability), and morning cravings.
3. Identify exclusions for self-treatment (Figure 47-2).	None
4 Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Recommend continued pharmacotherapy and counseling. Pharmacotherapy options include • Removal of nicotine patch at night and addition of a lozenge as needed (particularly in the morning upon waking). • Alternative NRT agent, such as lozenge alone. • Referral to PCP for prescription pharmacotherapy (nicotine inhaler, nicotine nasal spray, bupropion SR, varenicline). (2) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Because Ms. Brady has expressed that she thinks the patch is working well to manage her withdrawal symptoms, continue the nicotine patch, but advise her to take the patch off before bedtime. This change should help reduce the sleep disturbances and disturbing dreams. She can use combination therapy with a nicotine lozenge, as needed. The nicotine gum would not be a good choice because she has TMJ disease. A 2 mg lozenge dose to be used on an as-needed basis is reasonable.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"It's great that the patch is working for you so far. You have no contraindications or precautions for use of the nicotine patch and as-needed 2 mg lozenge. I have some ideas that should help you with your sleep problems and some other information for you, including how to manage morning cravings."

Relevant Evaluation Criteria	Scenario/Model Outcome
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	“You do not have any medical conditions for which nicotine replacement medications should be used with caution (e.g., recent heart attack, serious arrhythmias, angina). The nicotine patch provides a low, constant level of nicotine to help reduce nicotine withdrawal symptoms. By taking it off at night, you should no longer experience sleep disturbances. The nicotine lozenge should be used only when you experience situations in which you are craving a cigarette, such as when you wake up. Receiving counseling, in addition to taking your medications as directed, will increase your chances of quitting.”
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	
a. Appropriate dose and frequency of administration	“Use the 2 mg nicotine lozenge if you experience situations in which you are craving a cigarette, such as when you wake up.” (See Tables 47-5 and 47-8 .)
b. Maximum number of days the therapy should be employed	See Table 47-8 .
c. Product administration procedures	See Tables 47-7 and 47-9 .
d. Expected time to onset of relief	“With the lozenge, nicotine levels will peak 30-60 minutes after you start using it. You are already using the nicotine patch, which provides a steady amount of nicotine throughout the day. The blood nicotine levels from the patch and lozenge are lower than those from smoking, but they should be sufficient to help control your nicotine withdrawal. Most patients find that nicotine withdrawal symptoms peak in the first few days after the last cigarette; withdrawal symptoms then gradually diminish over the next 2-4 weeks.”

Relevant Evaluation Criteria	Scenario/Model Outcome
e. Degree of relief that can be reasonably expected	“Over time, you may find you need to use the lozenge less often. Be sure to stick with the recommended daily dosing schedule for the patch and the duration of use needed for the best chance of success. This will help you to be more comfortable while you are quitting.”
f. Most common adverse effects	“The most common adverse effects of the nicotine patch are skin reactions (redness, burning, and itching) at the application site and headaches. The sleep disturbances (vivid dreams and insomnia) that you are currently experiencing from the patch should resolve when you remove it before bedtime. The most common adverse effects of the nicotine lozenge are nausea, hiccups, and heartburn.”
g. Adverse effects that warrant medical intervention should they occur	“If you find that reducing your caffeine intake and using the nicotine lozenge do not help relieve your morning cravings and irritability during the day, contact your PCP. If you experience symptoms of nicotine excess (e.g., nausea, vomiting, dizziness, weakness, rapid heartbeat), also contact your PCP.”
h. Patient options in the event that condition worsens or persists	“Contact your PCP for the following reasons: You experience withdrawal symptoms or severe cigarette cravings. You may need a higher dosage of nicotine. You have adverse effects related to nicotine excess.” (see outcome in 8g.)
i. Product storage requirements	“Store the patches and lozenges at room temperature. Keep unused patches in the closed, protective pouch. Keep all new and used patches and lozenges out of the reach of children and pets.”
j. Specific nondrug measures	“Reduce caffeine use by half to minimize agitation and trouble sleeping. In addition to the counseling I can provide, other counseling programs are available, including the telephone quit line (1-800-QUIT-NOW), group classes, and internet-based programs. We can discuss which options you feel might be useful to you.”
Solicit follow-up questions from the patient or caregiver.	“How often can I use the lozenge?”
Answer the patient's or caregiver's questions.	“You should use the lozenge when you feel a strong craving to smoke, such as when you wake up in the morning. The patch will provide a consistent low level of nicotine to help reduce withdrawal symptoms. You should use the nicotine lozenge only when you feel a need, or urge, to smoke. Even though the box says you can use up to 20 lozenges a day, you should not need this many when you use them

Relevant Evaluation Criteria	Scenario/Model Outcome
	with the patch. Also remember to switch to the lower-strength 14 mg patch after 6 weeks; use it for 2 weeks, and then use the 7 mg patch for 2 weeks.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Confirm that Ms. Brady will reduce caffeine use, remove the patch before bedtime, and use the lozenge as needed for cravings. Call patient in 1 week to assess quit plan.

Key: NKA = No known allergies; NRT = nicotine replacement therapy; PCP = primary care provider; SR = sustained release; TMJ = temporomandibular joint.

Patient Counseling for Tobacco Cessation

Substantial benefits of quitting can be realized at any age. Although approximately 70% of adult smokers would like to quit,⁴ few are able to do so on their own. Research has shown that tobacco cessation rates can be substantially improved with treatment that includes counseling and pharmacotherapy.³¹ (See “Nonpharmacologic Therapy” for a detailed discussion of counseling.) Health care providers are in an ideal position to identify tobacco users and to either provide assistance throughout the cessation attempt or refer the patient to a tobacco cessation resource. The box “Patient Education for Tobacco Cessation” describes specific information to include in patient counseling.

Patient Education for Tobacco Cessation

Tobacco dependence is a chronic disease optimally treated with a

combination of counseling and medications. The primary goal of tobacco cessation treatment is to attain complete, long-term abstinence from all nicotine-containing products. For most people, carefully following product instructions and the self-care measures listed here will help ensure optimal treatment outcomes.

Nondrug Methods

- Receiving counseling from a health care provider will increase the success of tobacco cessation. A provider can help develop a tailored tobacco cessation treatment plan.
- Telephone quit lines (e.g., 1-800-QUIT-NOW) also are available to provide comprehensive counseling services at no cost.
- Internet-based resources and mobile apps also are available, many at no cost.

Nonprescription Medications

Nicotine Replacement Therapy (NRT)

- NRT helps relieve and prevent symptoms of nicotine withdrawal by partially replacing the high levels of nicotine that your body is used to obtaining from cigarettes. Use of NRT helps you to focus on changing your smoking routines and to practice new coping skills while decreasing your withdrawal symptoms.
- NRT does not contain any of the harmful tars and other toxins present in tobacco smoke.
- Symptoms of nicotine withdrawal are common and should subside over 2–4 weeks.
- Recommended daily dosages for NRT are shown in [Tables 47–5 and 47–8](#).
- See [Table 47–6](#) for usage guidelines for nicotine gum, [Table 47–7](#) for the nicotine lozenge, and [Table 47–9](#) for the nicotine patch.
- Carefully follow the dosage regimen for the selected product. Failure to do so will increase the chance of having withdrawal symptoms. Discontinuing therapy early might lead to relapse.
- Signs and symptoms of nicotine excess include nausea, vomiting,

dizziness, diarrhea, weakness, and rapid heartbeat.

- Do not eat or drink (except water) 15 minutes before or while using the nicotine gum or lozenge.
- Store NRT products at room temperature and protect from light.
- Keep new and used products out of the reach of children and pets.
- For all forms of NRT, consult your primary care provider before use if you have had a recent (in the past 2 weeks) heart attack, experience frequent pain caused by severe angina, have an irregular heartbeat, are pregnant or lactating, are younger than 18 years, or smoke fewer than 10 cigarettes a day.
- You may consider use of nicotine gum with the patch (gum used only on as-needed basis). For other possible medication combinations, speak to your primary care provider first.

When to Seek Medical Attention

- For all forms of NRT, stop use and seek medical attention if irregular heartbeat or palpitations occur, or if you have symptoms of nicotine overdose, such as nausea, vomiting, dizziness, diarrhea, or weakness.
- For nicotine gum: Stop use if mouth, teeth, or jaw problems develop.
- For nicotine lozenge: Stop use if mouth problems, persistent indigestion, or severe sore throat develops.
- For nicotine patch: Stop use if the skin swells, a rash develops, or skin redness caused by the patch does not subside with use of nonprescription hydrocortisone cream or does not go away after 4 days.

Evaluation of Patient Outcomes for Tobacco Cessation

Follow-up contact is an essential component of treatment for tobacco use and dependence.³¹ At each follow-up encounter, the provider should do the

following:

- Assess a patient's tobacco use status and, if appropriate, evaluate and monitor pharmacotherapy use.
 - Congratulate abstinent patients and encourage them to remain tobacco free.
 - In cases of relapse, review the specific circumstances, reassess the commitment to abstinence, encourage the patient to learn from identified mistakes, and identify strategies to prevent future lapses.
 - Determine whether the patient is experiencing nicotine withdrawal symptoms or adverse effects from the pharmacotherapy.
 - Offer ongoing support. If providing that level of support is not possible, refer the patient to a specialist for more intensive treatment.
-

Key Points for Tobacco Cessation

- Apply the 5 A's approach in providing tobacco cessation counseling: ask, advise, assess, assist, and arrange.
- For a patient who is not ready to quit, provide brief counseling, and emphasize that the pharmacist will be available when the patient is ready to quit smoking.
- For a patient who is ready to quit, offer counseling and pharmacotherapy. If time is limited, ask about tobacco use, advise the patient to quit, and refer the patient to the toll-free quit line (1-800-QUIT-NOW), web-based resources, mobile apps, and texting services.
- Numerous effective medications are available for tobacco dependence; encourage their use by all patients attempting to quit smoking—except when medically contraindicated or in specific populations for which evidence of effectiveness is insufficient (i.e., pregnant women, smokeless tobacco users, light smokers, adolescents). For patients with exclusions for self-treatment with NRT, referral to a primary care provider for further assessment is warranted.
- Advise patients that it is never too late for them to quit, but that

quitting earlier in life is clearly advantageous. Quitting smoking at any age has immediate as well as long-term benefits by reducing the risk for smoking-related diseases and improving health in general.

- The combination of counseling and medication for tobacco cessation is more effective than either alone.
- Smokers who quit can experience side effects from increased drug levels of several medications due to pharmacokinetic and pharmacodynamic interactions with tobacco smoke.
- It is essential that health care providers use the 5 A's counseling process to guide their patients through a quit attempt: ask, advise, assess, assist, and arrange. Patients also can be referred to the national quit line: 1-800-QUIT-NOW.
- Self-treatment is not recommended for those under the age of 18 years, someone who is pregnant or breastfeeding, and those with serious heart disease.
- Assess the tobacco user's smoking patterns and preferences to help determine an appropriate self-care strategy.
- Instruct patients on how to use the various nicotine replacement products, including application of the patch and the special chew and park technique for the gum.

Chapter 48: Home Testing and Monitoring Devices

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The home testing market continues to grow, offering an expanded array of products that are more user friendly and comprehensive. The global home diagnostics market is expected to increase from \$4.78 billion in 2017 to \$6.53 billion by 2025. The use of new technologies and wearable devices is fueling growth in several sectors. These tests typically are available as strips, cups, dip cards, cassettes, and, more recently, as digital monitoring devices. Blood, urine, and saliva are the primary testing media.¹

Forces driving the growth in home diagnostics include (1) increased public interest in health and preventive medicine; (2) reduced health care costs because patients can avoid unnecessary visits to health care providers and can seek earlier treatment of a medical condition; (3) reduced access and availability of health care resources; (4) increased number of available tests; and (5) important advances in technology that have led to simplified, accurate tests that can be easily performed at home.

Home testing and monitoring kits are designed to detect the presence or absence of a medical or physiologic condition and to monitor disease therapy. Recent growth in this market has been in the area of preventive health. Individuals with a family history of certain disorders, such as hypertension and diabetes, are using wearables and other devices as a proactive approach to monitoring the results of a wellness routine. Others who are interested in monitoring certain aspects of their health also are using wearables to obtain more personalized, individualized information to guide lifestyle and health decisions.

The Food and Drug Administration (FDA) requires home tests to perform as well as their professional-use equivalent. However, home tests must be used properly to achieve accurate results. The primary criterion for FDA approval of a direct-to-consumer test is the consumer's ability to obtain an accurate result and to interpret the result correctly; ultimately the test's benefits must outweigh its risks.² Throughout the approval process, the agency is looking for data and evidence that support the test's efficacy and its usability.³ FDA

maintains a website that provides information on approved nonprescription medical devices.²

This chapter discusses home test kits that aid in detecting the following disorders or conditions: pregnancy, female fertility; male fertility; colorectal cancer (fecal occult blood tests); high cholesterol levels; urinary tract infections; human immunodeficiency virus; hepatitis C; and drug abuse. This chapter also covers proper selection and use of blood pressure monitors, and provides a table of miscellaneous tests at the end of the chapter. For other products used in self-monitoring of disorders, see [Chapter 8](#) for discussion of self-treatment for vaginal fungal infections. Future home tests and diagnostics will be more complex and provide more data. These advances likely will lead to some patients feeling more empowered, others more confused, and many wanting guidance from a medical professional.

Selection Criteria

With the variety of diagnostic and monitoring products available, deciding which test to recommend to a given patient can be challenging. The major product variables to consider include test complexity, ease of reading results, presence of a control, and cost. [Table 48–1](#) addresses considerations for patients regarding the selection and use of home tests.

TABLE 48–1 Selection and Use of Home Tests and Devices

- Not all available tests are FDA-approved for home use. Check the status of a particular test at www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfiVD/Search.cfm.
- Always check the expiration date before purchasing a product to ensure that reagents are not outdated. For example, a test that has an expiration date of 04/2023 expires at the end of the designated month (April 30, 2023).
- Follow the manufacturer's instructions for storing the tests to ensure that reagents remain stable.
- When selecting a test, consider simplicity of use. Single-step tests usually are desirable because each step is a potential source of error.
- When considering cost, determine the cost per test unit and whether kits with multiple tests are needed. Generic or store-brand kits may cost significantly less.
- When possible, select a test that includes a control to ensure that the test is functioning correctly.
- Read all instructions carefully and completely before attempting to perform a test.

- Before scheduling or performing the test, note the time of day that the test is to be conducted, the length of time required, and any necessary supplies or equipment; then schedule the best time and place to conduct the test.
- Follow instructions exactly as described and in the order described. If you have questions about the testing procedure or interpretation of the results, consult a health care provider, or call the test manufacturer's toll-free number, if provided, for customer assistance.
- Use an accurate timing device that measures seconds to ensure that you wait the specified length of time between steps. Note that waiting longer than the specified time to read test results could affect test reliability.
- If the selected test requires observation of a color change, read the test in good lighting. If you have color-defective vision or other visual impairment, ask someone without vision difficulties to observe the color change and/or read the test results.
- If you have physical limitations that could interfere with performing the test, ask someone to help you perform the test.
- If the test requires a fingerstick and you have a medical condition or take medications that may cause excessive bleeding, consult your health care provider before performing the test.
- Food, medications, and certain diseases or conditions sometimes can interfere with test results.
- Many manufacturers offer the ability to navigate and interpret test results through portals. They also provide access to counselors/advisors/medical experts who can help with data interpretation and application.
- Discuss test results with your health care provider to ensure you take the appropriate actions based on your information and health status.

Key: FDA = U.S. Food and Drug Administration.

When recommending a test or device, the pharmacist must weigh the following potential variables:

- Is self-testing appropriate based on the patient's signs and symptoms?
- What is the patient's ability to accurately conduct the test? Interpret the results? Take appropriate actions based on the results?
- What happens if the test strip turns a specific color for a positive result, but the user is color blind?
- Is a "negative" result good or bad? Is a "positive" result good or bad?
- When should users contact their physician?
- What if a patient misinterprets the test results?
- What are potential interferences in obtaining accurate test results?
- Is there liability? Where/when does the manufacturer's responsibility

begin and end?

- What if patients take action on a result that leads to a poor outcome, uses an unapproved therapy, or seeks care from an unorthodox source that results in a negative outcome?
-

Pregnancy Detection Tests

Women now are able to detect pregnancy early, including before the day of the missed period because of the heightened sensitivity of at-home pregnancy tests. Early detection of pregnancy is desirable for many reasons, including allowing the woman to make decisions regarding prenatal care and lifestyle changes to avoid potential harm to the fetus.

Physiology of the Female Reproductive Cycle

The female reproductive cycle lasts approximately 28 days and is hormonally controlled. At the beginning of the cycle (day 1 through approximately day 12), low levels of circulating estrogen and progesterone cause the hypothalamus to secrete gonadotropin-releasing hormone (GnRH). In turn, GnRH stimulates release of the follicle-stimulating hormone (FSH) and low levels of luteinizing hormone (LH) from the anterior pituitary gland. This combination of hormones promotes development of several follicles within an ovary during each cycle. One follicle continues to mature while the others regress. At midcycle (approximately day 14 or 15), circulating and urinary LH levels significantly increase and cause final maturation of the follicle. *Ovulation* (rupturing of the follicle and release of the ovum) occurs approximately 20–48 hours after the LH surge. Cells in the ruptured follicle form the corpus luteum, which begins to secrete progesterone and estrogen. For approximately 7–8 days after ovulation, the corpus luteum continues to develop and secrete estrogen and progesterone, inhibiting further secretion of FSH and LH.

Once ovulation occurs, the ovum remains viable for fertilization for only 12–24 hours. Because sperm may live up to 72 hours, optimal days for fertilization to occur include the 2 days before ovulation, the day of ovulation, and the day after ovulation. For the greatest chance of achieving pregnancy, intercourse should take place within 24 hours after the LH surge.

If fertilization occurs, trophoblastic cells produce the human chorionic

gonadotropin (hCG) hormone. This hormone causes the corpus luteum to continue to produce progesterone and estrogen, forestalling the onset of menses while the placenta develops and becomes functional. As early as day 7 after conception, the placenta produces hCG, some of which is excreted in the urine. The concentration of hCG continues to increase during early pregnancy, reaching maximum levels 6 weeks after conception. The levels of hCG decline over the following 4–6 weeks and then stabilize for the remainder of the pregnancy.

If fertilization does not occur during a cycle, the corpus luteum degenerates, circulating levels of progesterone and estrogen diminish, and menstruation occurs (days 1–5). Resulting low levels of progesterone and estrogen cause release of GnRH from the hypothalamus, and the hormonal cycle begins again.

Usage Considerations

Numerous pregnancy tests with different reaction times and hCG sensitivity are available for home use. [Table 48–2](#) lists some available products that have been tested for accuracy.^{4–6} The most sensitive tests are capable of detecting hCG levels at the 20–25 mIU/hCG threshold. Factors to consider include accuracy based on testing a certain number of days before a missed period, time to obtain results, and how results are displayed.

TABLE 48–2 Selected Nonprescription Pregnancy Tests and Product Features

Trade Name (Website)	hCG Sensitivity ^a	Product Features
First Response Early Result ^b (www.firstresponse.com/en/product-listings/early-result-pregnancy-test)	<6.3 mIU/mL	• Uses test stick; digital display test also available • Best combination of sensitivity and reliability • Can test up to 6 days before missed period • Results obtained in 1 minute
Clearblue Plus/Advanced/Digital ^c	25 mIU/mL	• Uses test stick • Can test up to 5 days before missed period

Trade Name (Website)	hCG Sensitivity ^a	Product Features
		• Color-change tip indicates urine has been absorbed • Digital display test (50 mIU/mL) also available • Clearblue Advanced provides estimate of weeks since ovulation (1–2 weeks, 2–3 weeks, 3+ weeks) • Test strip technology prevents excess urine from causing error
Store-brand Products	25–50 mIU/mL	• Uses test sticks • Usually less expensive and possibly less reliable than brand-name products
E.P.T.	25–50 mIU/mL	• Uses test sticks • Digital display test also available
ClinicalGuard HCG Pregnancy Test Strips ^d (www.clinicalguard.com/pregnancy-test-guide)	25 mIU/mL	• Uses test strips (dip method) • Good option for those wanting to do multiple testing • Works well for women undergoing IVF
AccuMed Pregnancy Test Strips ^e (accumed.com/accumed-pregnancy-test-strips-25-count.html)	25 mIU/mL	• Uses test strips (dip method) • Works well for women with irregular periods • Can test as early as 5 days before missed period
Pregmate Pregnancy Urine Test Strips	25 mIU/mL	• Uses dip method for wide strip that is easy to use and read • Good option for multiple testing

Trade Name (Website)	hCG Sensitivity ^a	Product Features
		• Best if used no sooner than 1 day prior to missed period • Results obtained in 5 minutes
VeriClear Digital Early Result Pregnancy Test	10 mIU/ml	• Claims to detect pregnancy 6 days before missed period • Uses dip or midstream technique, with results provided in 3 minutes • Links to proprietary digital platform provided

^a Manufacturer's claimed sensitivity.

^b First Response Early Result Pregnancy Test [product information]. Church and Dwight Co, Inc., Ewing, NJ; 2020. Available at: <https://www.firstresponse.com/en/product-listings/early-result-pregnancy-test>. Accessed July 30, 2020.

^c ClearBlue Plus Pregnancy Test [product information]. SPD Swiss Precision Diagnostics, Geneva, Switzerland; 2020. Available at: <https://www.clearblue.com/pregnancy-tests>. Accessed July 30, 2020.

^d ClinicalGuard HCG Pregnancy Test Strips [product information]. Clinical Guard, Atlanta, GA; 2017. Available at: <https://www.clinicalguard.com/pregnancy-test-guide>. Accessed July 29, 2020.

^e AccuMed Pregnancy Test Strips. [product information]. Accumed, Houston, TX; 2020. Available at: <https://accumed.com/accumed-pregnancy-test-strips-25-count.html>. Accessed July 30, 2020.

Key: hCG = Human chorionic gonadotropin [hormone]; IVF = in vitro fertilization.

Mechanism of Action

Home pregnancy tests detect hCG in the urine by using monoclonal or polyclonal antibodies in an enzyme immunoassay. The antibodies are bound to a solid surface of the stick. If urinary hCG is present, it will form a complex with

the antibodies. Another antibody that is linked to an enzyme and that will react with a chromogen to produce a distinctive color is added. The hCG is sandwiched between the antibody linked to the enzyme and the antibodies bound to the solid surface. Filtering within the testing device removes unbound substances; a chromogen then reacts with the enzyme, causing a color change. Digital devices contain optical readers that provide results in words or icons.

Accuracy Rate

A pregnancy cannot be detected before implantation. Because of natural variability in the timing of ovulation, implantation does not necessarily occur before the expected onset of the next menses. One of the challenges with any home test is the ability for the user to accurately execute the testing process and evaluate the results. A study of 72 patients who used one of eight home-based pregnancy tests found that certain tests provided a greater chance of the user and a technician obtaining the same result. Clearblue Digital and Clearblue PLUS demonstrated >90% agreement; the percentage decreased for the products that are no longer available.⁷ An evaluation of test usability found most women preferred to use branded midstream digital and easy-use visual tests. Those ranking lower included store-brand tests, branded midstream visual tests, and cassette or strip tests.⁸

Another study found that 90% is the highest possible screening sensitivity for an hCG-based pregnancy test conducted on the first day of a missed period because 10% of women may not have an implanted embryo at that point. Although most pregnancy tests are advertised as 99% accurate on the day of the expected period, studies estimate that 97% is the highest possible screening sensitivity of a home pregnancy test performed by 1 week after the first day of the missed period.⁹ A test sensitivity for hCG of 12.4 mIU/mL is needed to detect 95% of pregnancies on the expected day of a missed period.¹⁰ The package insert for many tests now include a table that lists the accuracy rate based on the number of days before the expected period. The actual accuracy rate of these tests is lower because users do not carefully follow the directions; digital readouts, which are rated highly by users, appear to improve the patient's ability to use home pregnancy tests and to accurately interpret results.^{7,11}

The following recommendations are key to patients accurately performing the

test and interpreting the data:

1. Use first morning urine for the most accurate results.
2. Try to avoid getting up during the night to urinate. The test works best with “full bladder” urine because it will not be diluted.
3. Follow the guidelines for the test reaction time. Results read after the recommended time should be considered invalid because “false” lines may be present for a number of reasons after the specified reaction time. In this event, the results should be considered inaccurate, and the test should be repeated.

Interferences

A false-positive result may occur if the woman has had a miscarriage or given birth within the previous 8 weeks because hCG may still be present in the body. Medications such as Pergonal (menotropins for injection) and Profasi (chorionic gonadotropin for injection) can produce false-positive results. Unreliable results may occur in women who are perimenopausal or who have ovarian cysts or ectopic pregnancy. Oral contraceptive use does not affect test results.

A false-negative result typically is due to the user testing too early or the urine sample containing an inadequate level of hCG. If a test completed prior to a missed period yields a negative result, the woman should repeat the test in a week to verify the results.

Usage Guidelines

See the box “Patient Education for Pregnancy Tests.”

Product Selection Guidelines

Selecting the best test is based on three key benchmarks: test sensitivity, the ease of use/interpretation, and price. Product labeling for most tests states that women may use the test as early as the first day of a missed menstrual period. Some tests that can detect hCG levels at ≤ 20 –25 mIU/mL can be used 3 days before the missed period. The earlier a pregnancy test is used, the greater is the likelihood of a false-negative result. Most pregnancy tests are one-step procedures. Some tests have clear test sticks or a color change indicator that

allows the woman to see the reaction as it occurs; this feature serves as a check that the stick absorbed sufficient urine. Other products include two tests, which can be helpful if the first test is negative. The newest tests are digital and display the results as “Pregnant” or “Not pregnant,” or “Yes” or “No,” instead of showing colored lines, which eliminates the need to interpret the results. Test results generally are obtained in 3 minutes.

A study of seven nonprescription pregnancy tests found that First Response Early Result was the most sensitive and most reliable test. It detected hCG at concentrations as low as 6.3 mIU/mL. In addition, this product is expected to detect >95% of pregnancies on the first day of a missed period.¹²

Assessment of Pregnancy Test Use

Whether a pregnancy test is appropriate for a patient should be determined first by asking questions about her menstrual cycle and the number of days since intercourse. If product use is appropriate, the patient should be asked about her previous use of pregnancy tests and any difficulties she had with the tests. Questions about medical disorders and medication use also should be asked to determine whether inaccurate test results are possible or whether special measures may be required to protect the fetus.

Patient Counseling for Pregnancy Tests

During counseling on the use of pregnancy tests, the health care provider should emphasize the importance of following package instructions carefully, especially the instruction for when to begin testing. Pregnancy tests are very sensitive; therefore, the patient should be advised of medical and environmental factors that can cause inaccurate test results. It also is important for patients to pay close attention to expiration dating on the packaging, especially if the product has multiple test strips. The box “Patient Education for Pregnancy Tests” lists specific information to provide patients.

Patient Education for Pregnancy Tests

Usage Guidelines

- Unless package instructions specify otherwise, use the first morning urine because the levels of hCG, if present, will be concentrated at that time.
- If testing occurs at other times of the day, restrict fluid intake 4–6 hours before urine collection.
- Check the expiration date of the packaging. Remove test stick from packaging just before use. Remove cap from absorbent tip.
- Apply urine to testing device using whichever of the following methods is specified in package instructions: Hold test stick in the urine stream for designated time, or collect urine in a clean collection cup and dip the stick in the urine.
- After the urine is applied to the stick, lay the testing device on a flat surface. Wait the recommended time (1–5 minutes) before reading the results. Waiting the maximum allowed time may improve the sensitivity of the test.
- After reading the results, discard the testing device. If the test result is negative, test again in 1 week if menstruation has not started.
- Read all package labeling and inserts carefully for guidelines on how to complete the test, how many days before a missed period the test can be used, and how results are displayed.

Avoidance of Incorrect Results

- The most accurate results will be obtained by waiting at least 1 week after the date of the expected period. Performing the test earlier may produce false-negative results.
- Try to test the urine sample immediately after collection.
- If the sample must be tested later, store it in the refrigerator, but allow the sample to warm to room temperature for 20–30 minutes before testing. Chilled urine may produce false-negative results. Be careful not to redisperse or shake up any sediment present in the sample.

When to Seek Medical Attention

- If the second test is negative and menstruation has not begun, consult a health care provider.

- If you test positive, contact your health care provider as soon as possible to determine next steps.

Evaluation of Patient Outcomes With Pregnancy Tests

If the pregnancy test result is positive, the woman should assume that she is pregnant and contact her provider as soon as possible. In addition, if the patient is taking a medication that has teratogenic potential (e.g., Accutane, methotrexate) or any medications for chronic conditions, she should be advised to discuss with her provider any possible effects the medications may have on the fetus. If the test result is negative, the woman should review the procedure and make sure she performed the test correctly. She should test again in 1 week if her menses has not begun. If the results of the second test are negative and menses still has not begun, she should seek the advice of an appropriate health care provider.

Female Fertility Tests

Infertility is defined as the inability to become pregnant after having regular intercourse without birth control for 1 year in women younger than 35 years and for 6 months in women ages 35 years and older. *Primary infertility* is infertility in a woman who has never had a pregnancy. *Secondary infertility* is infertility in a woman who has had one or more pregnancies but cannot become pregnant again. Approximately 10% of women in the United States ages 15–44 years have difficulty becoming pregnant or staying pregnant, according to the Centers for Disease Control and Prevention. One-third of infertility cases are caused by fertility problems in women, another third are due to fertility problems in men, and the remaining cases are caused by a mixture of male and female problems or by problems that cannot be determined.^{13,14}

Basal body temperature (BBT) thermometers, ovulation prediction kits (OPKs), and devices to time sexual intercourse to coincide with optimal fertility can assist women in becoming pregnant. These tests and devices also are useful

for women who want to be more aware of their time of ovulation. However, they are not reliable methods for birth control.

Available nonprescription products for ovulation prediction include ovulation detection devices, BBT thermometers, and urine tests.^{15–20} Each detection method has a different mechanism of action and method of use. Many of the newer products are accompanied by a mobile app that downloads information and allows the user to analyze data compiled from built-in algorithms. More information about selected products and key features is provided in **Table 48–3**. Women should select their preferred method, but health care providers are encouraged to become actively involved in educating women on the pros and cons of each option and in assisting with the selection process.

TABLE 48–3 Selected Nonprescription Ovulation Prediction Tests and Devices and Features

Trade Name (Website)	Product Features
OvuSense vaginal temperature sensor ¹⁵ (www.ovusense.com/us)	• Ovusense sensor inserted into vagina overnight; measures CBT every 5 minutes • Sensor removed and cleaned in the morning before downloading of data to the Ovusense App • Data uploaded to secure cloud database • Used for two cycles to obtain data for “short range” 4-day ovulation window • Can alert user up to 24 hours before ovulation based on in-cycle data • Can compare ovulation dates and cycle pattern by scrolling on app • Real-time data shared through app • 99% claimed accuracy rate for detecting ovulation date
NaturalCycles ¹⁶ (www.naturalcycles.com)	• Thermometers and mobile application • Pairs BBT monitoring with algorithm that uses patient cycle information to predict fertile window • Patient takes AM temperature; enters data into app • Can add menstrual period data for more accurate prediction • Can add extra information, including cycle symptoms, mood changes, sexual intercourse data

Trade Name (Website)	Product Features
	• 99.5% accuracy in identifying fertile days
Ava Sensor Bracelet¹⁷ (www.avawomen.com)	• Patient wears Ava Sensor Bracelet to bed • Measures skin temperature changes, pulse rate, heart rate, perfusion, respiratory rate • Measures datapoints 25 times per second • Device synced each morning • App takes data and identifies 5 best fertile days • Tested for women who have cycles of 24–35 days • Not to be used in patients with PCOS or irregular cycles • 12-hour rechargeable battery • 50% more accurate than traditional calendar method
OvaCue Fertility Monitor¹⁸ (www.fairhavenhealth.com/product-category/fertility/ovulation-prediction/)	• Hand-held fertility monitor with saliva and cervical mucus sensors; requires a few seconds for each daily test • Measures estrogen-induced changes in the electrolyte levels in saliva and cervical mucus • Monitor tracks trends and attempts to identify a specific trend (“cue peak”) that marks the beginning of the fertile window • Once cue peak detected, monitor identifies dates of low to peak fertility, providing 5–7 days advance notice of ovulation • Data uploaded to OvaGraph using USB cable (included); stores up to 4 months of readings • Can be used by women with irregular cycles and PCOS • Interprets each user reading in relation to previous user readings • Comes with access to OvaGraph, a full-featured fertility charting tool • Access to OvaCue specialists at Fairhaven Health provided to assist with data interpretation • Can share charts with health care providers • Technology shown to be >98% accurate in NIH-funded studies

Trade Name (Website)	Product Features
iFertracker Smart Fertility Tracker¹⁹ (www.ifertracker.com)	• Wearable fertility tracker • Synced via Bluetooth with app; device gathers continuous BBT data while user sleeps • Automatically charts data and provides user with daily fertility snapshot • Built-in algorithm filters out events that have thermal impact on BBT • Sensor placed directly beneath crease of armpit; daily site rotation recommended • Device identifies invalid data (e.g., mid-night arisings) and accommodates variations in sleeping schedules • Collects 20,000 data points per night • Notifications provided for optimum times for conception • BBT chart can be exported directly from app • Testers encouraged to use mobile app's health log to record moods, stress, sexual activity, cervical mucus quality, and sleep to increase accuracy of ovulation prediction feature • Temperature accuracy within 0.05°C and 0.09°F
Mira Analyzer and App²⁰ (www.miracare.com)	• Combines tracking of hormonal and menstrual patterns with learning algorithm and smartphone connectivity • Provides quantitative hormone measurements and predicts ovulation/fertility window • Tracks LH and estrogen levels • Works in women with irregular cycles, PCOS, or hormone imbalance • Allows entry of full suite of additional fertility tracking data (e.g., intercourse and menstrual period dates, cervical mucus levels, cervical anatomy, BBTs) • Offers advanced algorithm that provides personalized and accurate insight for fertility window • 99% accuracy rate
Clearblue Fertility Monitor with Touch Screen (www.clearblue.com/ovulation-tests/fertility-monitor-with-touch-screen)	• Designed to identify all fertile days • Used with Clearblue Test Sticks (sold separately)

Trade Name (Website)	Product Features
	• Urine collection via midstream or dip (suggested) methods • Test stick inserted into device; results provided in 5 minutes • Touch Screen technology with alarm reminder, calendar, and ability to record other data (e.g., dates for menstrual cycles and sexual intercourse) • Measures LH and E3G levels • Provides three ranges for fertility status: low, high, peak • Stores up to six cycles of data that can be shared with physician • 97% consistency with ultrasound
Clearblue Connected Ovulation Test System (www.clearblue.com/ovulation-tests/connected-ovulation-test-system)	• Measures LH and E3G levels • Identifies ≥ 4 fertile days • Reusable holder for test sticks • Results provided in 5 minutes • Urine collection via midstream or dip (suggested) method • Connects via Bluetooth to smartphone • Smart reminders for best days to test based on personal data
Clearblue Advanced Digital Ovulation Test (www.clearblue.com/ovulation-tests/advanced-digital)	• Urine collection via midstream or dip (suggested) method • Test stick inserted into device; results provided in 5 minutes • Measures both LH and E3G levels • Identifies ≥ 4 fertile days • Reusable holder/reader for the test sticks • Algorithm adapts to user's hormone profile
Clearblue Easy Ovulation Kit (www.clearblue.com/ovulation-tests/easy-ovulation-kit)	• Urine collection via midstream or dip (suggested) method • Test stick (absorbent tip) plus result window included • Results provided in 3 minutes • Measures only LH level • Identifies 2 most fertile days

Trade Name (Website)	Product Features
	• Results indicate “Yes” or “No” for LH surge • Includes one pregnancy test
Clearblue Digital Ovulation Test (www.clearblue.com/ovulation-tests/digital)	• Urine collection via midstream or dip (suggested) method • Test stick inserted into device; results obtained in 3 minutes • Measures only LH level • Identifies 2 most fertile days • Digital smiley face technology to identify LH surge • Reusable holder/reader for test sticks
First Response Ovulation Plus Pregnancy (www.firstresponse.com/en/product-listings/ovulation-plus-pregnancy-test)	• Urine collection via midstream or dip method • Identifies 2 most fertile days • Measures LH level only • Results provided in 5 minutes • Includes one pregnancy test

Key: BBT = Basal body temperature; CBT = core body temperature; E3G = estrone-3-glucuronide; LH = luteinizing hormone; NIH = National Institutes of Health; PCOS = polycystic ovarian syndrome; USB = universal serial bus.

Basal Thermometry

For many years, women have measured their BBT to predict the time of ovulation. Resting BBT usually is between 97.0°F (36.1°C) and 97.5°F (36.4°C) during the first part of the female reproductive cycle. Approximately 24–48 hours after ovulation, it rises to a level closer to normal (i.e., 98.6°F [37.0°C]).²¹

Usage Considerations

Mechanism of Action

When using basal thermometry, women take their temperature (orally, rectally, or vaginally) with a basal thermometer each morning before arising. These temperature measurements are then plotted graphically. A rise in

temperature signals that ovulation has occurred. When the increase occurs, women who want to become pregnant should have intercourse as soon as possible to maximize their chances of conception.

Accuracy Rate

The only equipment necessary for monitoring BBT is a basal thermometer, which has smaller gradations than a regular thermometer (i.e., 0.1 degree vs. 0.2). Although basal thermometry is a relatively simple method of ovulation prediction, interpreting temperature data can be confusing. The temperature increase that follows ovulation is small (0.4°F–1.0°F [0.2°C–0.6°C]). Women who have trouble reading a thermometer may miss the rise altogether; in this case, a digital model should be used.

Interferences

Several factors, such as emotions, movements, and infections, can influence the BBT. Eating, drinking, talking, and smoking within 30 minutes of checking one's temperature should be postponed until after a measurement is obtained.

Usage Guidelines

See the box “Patient Education for Ovulation Prediction Tests and Devices.”

Product Selection Guidelines

Digital thermometers that track multiple temperature readings for the user are available, although they are more expensive than digital thermometers that lack this feature.

Urinary Hormone Tests

Ovulation prediction tests that use urine samples to estimate the time of ovulation are marketed to women who are having difficulty conceiving and need to pinpoint ovulation. Most of these products determine ovulation by detecting the urinary LH level, and some also have the ability to assess the presence of estrone-3-glucuronide (E3G), a component of estrogen. E3G levels rise and fall in a pattern similar to that of LH but peak sooner, thus expanding the window of detection.

Usage Considerations

Mechanism of Action

Urine-based ovulation prediction tests use antibodies specific to LH to detect the surge in its level. An enzyme-linked immunosorbent assay (ELISA) elicits a color change that indicates the level of LH in the urine. The LH surge is revealed by a difference in color or color intensity from that noted on the previous day of testing. The intensity of color on the test stick is directly proportional to the quantity of LH in the urine sample. The standard digital test has a similar mechanism of action: When LH is detected in urine, the test stick shows a blue surge line that is read by the digital device. The digital device will display a smiley face, which means that LH has been detected and that a woman's chances for conceiving are increased over the next 48 hours. This device also sets an individualized threshold for measuring the user's LH readings and compares them from baseline. The digital device helps to decrease human error. Generally, early morning collection of urine is recommended because the LH surge usually begins early in the day, and the urine concentration is relatively consistent at this time. Some products do not specify a time of day and require only that a consistent time of day be used.

Testing should begin 2–4 days before the estimated day of ovulation. The kit contains directions to determine when to begin testing; the starting date is based on the average length of the past three menstrual cycles. If the cycle varies by >3–4 days each month, the woman should use the shortest menstrual cycle to determine the starting date.

A study comparing pregnancy rates in women who used an ovulation prediction system with those who did not use a system was conducted. The proportion of women who used an application-connected ovulation test system that measured both LH and an estrogen metabolite and who became pregnant after one cycle was significantly greater (25.4%) than for women who did not use a testing system (14.7%; $P < 0.001$). After two cycles this trend continued: 36.2% for those using the system versus 28.6% for those not testing; $P = 0.026$.²²

Surveys of those who used a home digital ovulation test reported positive experiences (ovulation confirmation, better understanding of the menstrual cycle) and negative experiences (uncertainty about results, changes in their

relationship with their partner, emotional consequences). The survey also found that women trying to conceive want access to high-quality information about the use of these tests and the results.²³ Other studies found that use of these tests did not significantly impact the user's stress levels. (See the section "Product Selection Guidelines" for further information.)

The Clearblue Advanced Digital Ovulation Test and the Clearblue Fertility Monitor test increase the window for ovulation detection by measuring the hormones LH and E3G, a component of estrogen. The advanced digital product uses a test holder and disposable test sticks that are inserted into the holder for reading. The test holder contains special software that tracks changes in a woman's hormone levels from baseline to display peak and high fertility trends. The Clearblue Fertility Monitor with Touchscreen is a palm-size device with a light-emitting diode screen that allows the woman to insert a test stick into the monitor to obtain results. To accurately predict ovulation, the patient must establish a baseline using data about fluctuations in her hormone levels. For the first month, the test monitor will instruct the woman to test daily for 10–20 consecutive days, starting on approximately the sixth day after the beginning of menstruation. Using these data, the monitor calculates the time window for optimum chances of conception. After establishing her baseline, the woman tests for 10–20 days each month, depending on her cycle length. Each day's results are displayed as "low," "high," or "peak fertility." A low result indicates a small chance of conception; a high result indicates an increased chance of conception. The reading typically is displayed for 1–5 days, leading up to the peak fertility period for each cycle. A peak fertility reading indicates the highest chance of conception and usually is observed 2 days before ovulation.

When compared with no use of a detection method for ovulation, another test, the Clearblue Connected Ovulation Test System, was shown to double a woman's chances of getting pregnant in the first cycle of use. The product identifies 4 or more fertile days each cycle and tracks two key fertility hormones (E3G and LH). During testing, the product connects via Bluetooth to a smart phone, and the results are synced and displayed on the phone. The provided calendar and cycle comparison charts allow the user to set smart reminders.²⁴

Data evaluating common devices showed that the Clearblue Easy Fertility Monitor with Touch Screen reported a significantly higher pregnancy rate

during the first two cycles in women using this product compared with control groups (22.7% vs. 14.4%). The manufacturer claims this testing device and the Clearblue Digital Ovulation Test, which features a dual hormone indicator, can identify 4 or more fertile days with an accuracy rate of >99% and with a sensitivity to determine ovulation of 97%. Both monitors are digital immunoassays incorporating a disposable microspectrophotometer.²⁵

Interferences

Medications used to promote ovulation (e.g., menotropins) artificially elevate LH levels and may cause false-positive results in ovulation prediction tests that measure only LH. The true LH surge can be detected in patients receiving clomiphene as long as testing does not begin until the second day after the drug therapy ends. Medical conditions associated with high levels of LH, such as menopause and polycystic ovarian syndrome (PCOS), may cause false-positive results for ovulation. Pregnancy also can cause a false-positive result for ovulation. If the patient has recently discontinued using oral contraceptives, the start of ovulation may be delayed for one to two cycles. Therefore, it would not be appropriate to use a home ovulation prediction test until fertilization has been attempted unsuccessfully for 1–2 months after discontinuation of the use of oral contraceptives.

The presence of PCOS; medications that affect the cycle (e.g., oral contraceptives, certain fertility treatments, estrogen-containing medications); impaired liver or kidney function (which alters levels of E3G); breastfeeding; tetracycline; and perimenopause may produce false-positive results with the Clearblue Fertility Monitor. Women who have been pregnant recently, stopped breastfeeding, or stopped using hormonal contraception should consider waiting until they have at least two consecutive natural menstrual cycles (lasting 21–42 days) before using this product.

Usage Guidelines

See the box “Patient Education for Ovulation Prediction Tests and Devices.”

Product Selection Guidelines

The available ovulation prediction tests vary in the length of time needed to complete the test, method of applying urine to the test stick, number of individual tests provided, and method for reading results. Patients with longer

cycles may benefit from purchasing kits that contain more testing sticks. One of the concerns expressed by some patients and providers is the added stress involved with using an ovulation testing system. Two studies determined that the use of a digital home ovulation test did not increase the level of stress in women trying to conceive. Of note, the authors did attempt to remove the potential bias related to the percentage of women in each group (study and control) who conceived.^{26,27}

The advantages of OPKs include

- They are easy to use.
- They provide information about the approach of ovulation.
- They accurately predict ovulation: 80% accurate with 5-day testing; 95% accurate with 10-day testing.
- They can be combined with other methods, such as BBT.
- Although ideal, they do not require testing of the first urine in the morning. Directions suggest testing within the same 6-hour window each day to obtain the most accurate results.²⁸

The disadvantages of OPKs include

- Regular testing is costly.
- Results could be difficult to interpret if the LH surge is low.
- They are not the most accurate system for women with PCOS.
- They cannot be used to confirm ovulation because an LH surge with no egg release can occur.
- No results are provided if testing is done too early or when the woman is not ovulating.

The Clearblue Fertility Monitor and Clearblue Advanced Digital Ovulation Test have some possible advantages over the traditional ovulation prediction kits, which detect only LH levels. The traditional kits identify the 24- to 48-hour window around ovulation. Both Clearblue products identify a larger window of several days and do not require that patients interpret color changes. In addition, these products measure both LH and E3G levels, increasing the specificity of ovulation prediction. However, no studies have proved that these advantages increase a woman's chance of accurately identifying ovulation and, ultimately, conceiving. Compared with the traditional ovulation prediction kits, which detect only LH levels, the initial cost of the Clearblue Fertility Monitor with Touchscreen is higher, but it is reusable for an indefinite period, with only

the additional expense of purchasing more test sticks.

Assessment of Female Fertility Test Use

The patient should be asked privately about her reasons for using an ovulation prediction test. If the reason is difficulty in conceiving, the patient should be asked whether she has consulted a health care specialist about a possible fertility problem and whether she has previously used ovulation prediction tests or devices. Questions about other possible pathology and medication use are appropriate to determine possible interferences with test results or temperature measurements. Case 48–1 illustrates assessment of a patient who wishes to become pregnant.

Case 48–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient has been trying to become pregnant for 2 months. She asks if the ovulation kits can help.
b. Medical history, including family history	Menstrual cycle: 29 days; regular cycle in the past. She has regular intercourse with her husband of 3 years.
c. Patient's identity	Cherise Turner
d. Patient's age, gender, height, and weight	31 years old, female, 5 ft 6 in., 145 lb
e. Patient's occupation	School assistant principal
f. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	No current medical conditions; multivitamin and probiotic daily

Relevant Evaluation Criteria	Scenario/Model Outcome
g. Prior use of diagnostic/monitoring test	Has never used any home diagnostic tests.
h. Potential problems with performing/interpreting test	Cherise does not know how to use an ovulation prediction test.
Assess	
2. Determine whether self-testing is appropriate.	Self-testing is appropriate.
3. Identify exclusions for self-treatment.	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Recommend an ovulation test today. Educate the patient to follow all manufacturer's instructions when performing the self-test. (2) Advise the patient to make an appointment with her HCP if she does not become pregnant within 1 year. (3) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Because the patient likes technology, she is interested in trying a fertility monitor.
Implement	
6. Describe the testing procedure to the patient.	
a. Specific instructions	"When you perform the test, follow the instructions carefully."
b. How to avoid incorrect results	See the box "Patient Education for Pregnancy Tests."

Relevant Evaluation Criteria	Scenario/Model Outcome
Solicit follow-up questions from the patient or caregiver.	“How long should I do the tests before seeing a doctor?”
Answer the patient’s or caregiver’s questions.	“It can take up to a year for couples to conceive without the help of ovulation prediction. If you are able to predict ovulation consistently with the monitor for 3 months and have not become pregnant, you should make an appointment with your health care provider.”
Follow-up: Monitor and Evaluate	
7. Assess patient outcome.	“You can call if you have any questions while doing the test or are concerned about the results.”

Key: HCP = Health care provider.

Patient Counseling for Female Fertility Tests

To use ovulation prediction products effectively, a woman must know approximately when ovulation occurs or be willing to track three menstrual cycles to determine when it occurs. The health care provider should explain hormonal fluctuations during the cycle and how they relate to the use of ovulation prediction tests and devices. The provider also should explain the reason for the number of tests or measurements that must be performed with each type of product. Finally, counseling should emphasize consistent use of the products for at least 3 months to achieve accurate results. The box “Patient Education for Ovulation Prediction Tests and Devices” lists specific information to provide patients.

Evaluation of Patient Outcomes With Female Fertility Tests

Ovulation prediction products should not be used for >3 months. If conception does not occur within this period, the woman should see a health care provider.

Patient Education for Ovulation Prediction Tests and Devices

Basal Body Temperature (BBT) Thermometers

Usage Guidelines

- Read the instructions thoroughly before using the thermometer.
- Choose one method of taking temperatures (orally, vaginally, rectally; review product labeling for specific recommendations), and use that method consistently.
- Take temperature readings at approximately the same time each morning. Take temperature just before rising each morning after at least 5 hours of sleep. If using a regular basal thermometer, plot the temperatures on a graph. A rise in temperature indicates that ovulation has occurred.

Avoidance of Incorrect Results

- Do not move while taking temperature measurements.
- Note that emotions can affect temperature measurements.
- If fever is present, discontinue the measurements until the fever is resolved. Resume measurements on the first day of the menstrual cycle that occurs after the fever is gone.
- Do not eat, drink, talk, or smoke within 30 minutes of taking temperature measurements.

Ovulation Prediction Tests

Usage Guidelines (Except Clearblue Fertility Monitor With Touch Screen)

- Start using the test 2–3 days before ovulation is expected.

- Follow the manufacturer's specific directions for the timing of urine collection. If the first morning urine is not tested, restrict fluid intake for at least 4 hours before testing. Avoid urinating until you are ready to test the urine so that the urine will not be diluted.
- Test the urine sample immediately after collection.
- If immediate testing is not feasible, refrigerate urine for the length of time specified in the product's directions. Allow refrigerated sample to stand at room temperature for 20–30 minutes before beginning the test.
- Do not shake up any sediment that may be present in the sample.
- Either hold a test stick in the urine stream for the specified time, or collect urine in a collection cup and dip the stick in the urine.
- After the urine is placed on the testing device, read the results in 3–5 minutes, depending on the manufacturer's instructions.
- Watch for the test's first significant increase in color intensity or, if using a digital test, the display of an indicator, such as a 'smiley face', suggesting a result. Either result indicates that the surge of LH has occurred and that ovulation will occur within 1 or 2 days.
- Once the LH surge is detected, discontinue testing. Remaining tests can be used later, if necessary.
- If the LH surge is not detected, carefully review the testing instructions to ensure that they were performed properly.
- If the testing procedure was accurate, ovulation may not have occurred or testing may have occurred too late in the cycle. Consider testing for a longer period and earlier in the next cycle to increase the chances of detecting the LH surge.
- Many tests now come with an app or other technology that complements the actual test to improve predictability.

Usage Guidelines for Clearblue Fertility Monitor With Touch Screen test

- For the first month, begin testing on the sixth day after menstruation starts; the monitor will indicate how many total days you should test.
- For subsequent months, test the number of days indicated by the monitor.
- Remove test stick from packaging just before use.

- Hold the test stick in the urine stream; insert stick in monitor.
- Discard test stick after use.

Avoidance of Incorrect Results

- Fertility medications, PCOS, menopause, and pregnancy can cause false-positive results for ovulation. Note: Some tests can be used by patients who have PCOS. If applicable, package labeling should provide this information.
- With the Clearblue Fertility Monitor With Touch Screen, estrogen-containing medications, impaired liver or kidney function, breastfeeding, tetracycline, and perimenopause can cause false-positive results.
- Recent pregnancy or discontinuation of oral contraceptives or breastfeeding will delay ovulation for one or two cycles. Start testing after two natural menstrual cycles have occurred.

When to Seek Medical Attention

- If a negative test is obtained or there are questions about any test result, see a health care provider for evaluation and further testing.

Key: LH = Luteinizing hormone; PCOS = polycystic ovarian syndrome.

Male Fertility Tests

Infertility affects an estimated 15% (48.5 million) of couples globally. Males are found to be solely responsible for 20%–30% of infertility cases and contribute to 50% of cases overall; 12% of men worldwide are infertile and may not know it.²⁹ Sperm concentration is one of the many factors used to determine male fertility. Because many additional factors play a role in male infertility, a positive test for sperm count is not a guarantee of fertility. A decreased sperm concentration is known to result from epididymitis, orchitis, hormone imbalances, anabolic steroid use, smoking, heavy alcohol use, and diabetes. A systematic review and meta-regression analysis of data from 1973 to 2011 that

looked at recent trends in sperm counts (concentration and total count) found a significant decline in both measures. Specifically, there was a 50%–60% decline among men unselected by fertility from the following geographic areas: Australia, Europe, New Zealand, and North America.³⁰

Usage Considerations

The available male fertility tests measure sperm concentration within ranges, usually low (<15 million [M]/mL), moderate (15 M/mL–55 M/mL), and optimal (>55 M/mL). The low fertility range differs slightly from the World Health Organization (WHO) cutoff value of 20 M/mL.³¹ Test results suggesting male infertility are manufacturer specific, so users are encouraged to review the manufacturer packaging and insert information carefully. In most cases, at least two test results are needed to validate a man’s status. Some tests also assess sperm volume, motility, and morphology, which may be important variables in assessing fertility status.

Mechanism of Action

Multiple tests are available to assess sperm count (Table 48–4). The Spermcheck Fertility semiquantitative test works by detecting the concentration of a sperm-specific protein (antigen SP-10) in the semen, which is then used to determine the sperm count. The semen is mixed with a buffer to help release the specific protein from the sperm. The mixture then binds to a colloidal gold compound in the test well and flows through the test. If the sample contains 20 million or more cells per milliliter, a reddish line appears, indicating a positive result. The test kit contains all the necessary supplies for the test: a testing device, testing solution, transfer device, and sperm collection cup.³²

TABLE 48–4 Selected Nonprescription Male Fertility Tests and Devices	
Trade Name (Website)	Product Features
Trak Male Fertility Testing System (trakfertility.com/)	• Tests for sperm count and semen volume • Measures sperm count as Optimal: >55 M/mL; Moderate: 15–55 M/mL; or Low: <15 M/mL • Includes reusable Trak Engine, two sperm count tests, and two semen volume tests.

Trade Name (Website)	Product Features
	• Semen sample collected in provided cup • Sample loaded into a test Prop and attached to Engine • Sample “spun”; sperm count results provided after 6 minutes • Sperm volume also assessed based on comparison of actual results to WHO standards
myLab At Home Male Fertility Test www.mylabbox.com/at-home-std-kits/fertility/; www.yospermtest.com/#)	• Includes two rapid tests • Measures motile sperm concentration, motility, and morphology • Provides results in one of three ranges: Optimal: >55 M/mL; Moderate: 15–55 M/mL; or Low: <15 M/mL • Quality score and fertility improvement app • Video provided • YO Home Sperm Test Kit provided via partnership between myLab and Medical Electronic Systems • Takes approximately 30 minutes to obtain results • Testing twice recommended to establish baseline for measuring progress; then testing at least monthly outside partner’s fertile window recommended • >97% accuracy rate in clinical trials
SpermCheck Fertility Home Sperm Test www.spermcheck.com/fertility/product-info/)	• Sample collected at home; must sit for 20 minutes • All necessary supplies included • Semen sample mixed with proprietary solution; mixture is added to SpermCheck Fertility Device for analysis • Takes approximately 10 minutes to complete remaining steps and receive results • Positive (normal) results: sperm count ≥ 20 M/mL; negative (low) results: sperm count <20 M/mL
Fellow Kit for semen analysis³⁷ www.meetfellow.com)	• Test purchased from manufacturer’s website

Trade Name (Website)	Product Features
	• Physician network reviews and approves purchase • Test completed at home; results sent to patient and, if requested, patient's physician • Tests for sperm motility, morphology, count, volume, and concentration • Completed test mailed to CLIA-certified laboratory • Results provided within 10 days of laboratory's receipt of completed test • Lifestyle recommendations provided to ensure accuracy of test results

The Trak Male Fertility Testing System is a quantitative assessment of sperm concentrations of ≥ 15 M/mL, which is within the three ranges specified earlier. Semen is collected and loaded into the proprietary centrifugal device that uses density gradient separation to isolate sperm from the sample. The sample is spun to filter contaminants; then it is sent to a metering chamber where results are visible in a column corresponding to one of the three concentration ranges. The Trak Testing System contains all necessary supplies for the user to complete two tests; supplies can be purchased for additional tests.^{33,34}

The YO Home Sperm Test Kit, the test kit promoted by myLab as the myLab At Home Male Fertility Test, is used with the proprietary software application to provide a qualitative assessment of motile sperm concentration (MSC). A semen sample is collected, liquefied with eosin and chymotrypsin, and then pipetted onto a cover-slipped slide. This slide is inserted into the YO clip that is attached to the user's smartphone. The test measures MSC as either low (< 6 M/mL) or moderate/normal (≥ 6 M/mL). The kit comes with all the necessary supplies to conduct two tests; additional supplies can be purchased and used with the already-purchased technology.^{35,36}

The Fellow Kit for Semen Analysis is a system for at-home sample collection that is mailed to a Clinical Laboratory Improvement Act (CLIA)-certified laboratory for analysis. The sample is analyzed for sperm motility, morphology, concentration, volume, and count. Results usually are provided within 10 days

of sample receipt, and the manufacturer's physician network is available to assess the data and provide recommendations.³⁷

Accuracy Rate

Testing performed by the various manufacturers and independent researchers found the overall accuracy of the various tests to be between 82.4% and 98%.^{32,34-36}

Interferences

No interferences that can cause false positive or negative results are known.

Usage Guidelines

See the box "Patient Education for Male Fertility Tests."

Product Selection Guidelines

Multiple male fertility tests are currently on the market. Because some tests require the user to determine visually whether a line is present, patients with visual difficulties should seek assistance in interpreting the test results. Those more comfortable with a process completed entirely in their home can select one of several products; others who wish to use a CLIA-certified laboratory have that option.

Assessment of Male Fertility Test Use

The patient should be asked privately whether he has consulted a health care provider about a possible fertility problem and whether he has previously used male fertility tests.

Patient Counseling for Male Fertility Tests

The patient should be advised that most of these tests do not account for sperm motility, morphology, and other factors that contribute to male fertility. The box "Patient Education for Male Fertility Tests" lists specific information to provide patients.

Evaluation of Patient Outcomes With Male Fertility Tests

If a negative result is obtained, the patient should contact his health care provider or a fertility specialist. If a negative result is obtained but the patient is trying to increase his sperm count, he can test his fertility on a more regular basis, usually recommended as every 3 months.

Patient Education for Male Fertility Tests

Usage Guidelines

- The semen sample is collected by masturbation, with semen directed into the provided collection cup or container.
- Each manufacturer has very specific processes that must be followed. The following are for the more commonly used male fertility tests:

SpermCheck Kit

- Because freshly ejaculated semen is gel-like, the sample must be allowed to sit for 20 minutes, during which it will thin to a liquid consistency for testing.
- Gently stir the cup with the semen transfer device at least 10 times.
- Insert the semen transfer device into the sample cup, and withdraw semen to the level of the black line, while trying to avoid creating any air bubbles.
- Gently add the semen to the upright SpermCheck solution bottle. Gently mix the solution by turning the bottle upside down at least 5–10 times. Let the solution bottle stand for 2 minutes before completing the next step.
- Add 6 drops of the solution to the sample well on the SpermCheck device that is labeled “S.”
- Read results exactly 7 minutes after adding the solution.
- To read the test, make sure there is a reddish line beside the “C” (Control) position on the device. If a control line is not present, the

test did not work accurately. If a reddish line appears next to the “T” (test) position on the device, the result is positive (sperm ≥ 20 million/mL). If no line is present at the test position, the sample is negative (sperm ≤ 20 million/mL). Do not compare the faintness or darkness of the lines between the control and test positions. The presence of a line is a positive test result.

YO Sperm Kit

- Collect semen sample in the provided cup.
- Add liquifying powder to the sample; sample may turn a pinkish color.
- Wait 10 minutes to ensure that the liquification process is complete.
- Attach the YO Clip (provided in the kit) to your smartphone.
- Withdraw some of the sample from the cup using the pipette provided.
- Apply the sample onto the YO slide in the designated area.
- Insert the slide into the YO Clip.
- Tap “Start Testing” and results will be provided in 2–3 minutes.
- Provides results in 1 of 3 ranges: Optimal: >55 M/mL; Moderate: 15–55 M/mL; or Low: <15 M/mL.

Trak Male Fertility Testing System

- Collect a semen sample in the cup provided in the kit.
- Load sample into the test Prop, and attach the Prop to the Engine.
- Sample will be “spun”: after 6 minutes, the sperm count results are provided.
- Test measures sperm count as Optimal: >55 M/mL; Moderate: 15–55 M/mL; or Low: <15 M/mL.

Avoidance of Incorrect Results

- Collect a semen sample between 2 and 7 days after the last ejaculation.
- Test as soon as possible after sample collection.

When to Seek Medical Attention

- If a negative test is obtained, see a health care provider for evaluation and further testing.
- If an optimal test result is obtained but pregnancy is not achieved after 1 year, see a health care provider.

Fecal Occult Blood Tests

Colorectal cancer (CRC) is the second most common cause of cancer death in the United States. Every 3 years, the American Cancer Society provides an update of CRC occurrence based on incidence data (available through 2016) from population-based cancer registries and mortality data (through 2017) from the National Center for Health Statistics. In 2020, approximately 147,950 individuals will have been diagnosed with CRC, and 53,200 will have succumbed to the disease. Data suggest that those in the screening-age groups (see the section “Assessment of Fecal Occult Blood Test Use”) saw declines in incidence and mortality. An increase in access to guideline-recommended screening will enhance progress against CRC.³⁸

One early and common symptom of CRC is bleeding. Checking for hidden (occult) blood in the stool is an easy way to screen for a potential colon problem. Fecal occult blood tests (FOBTs) can be used as an adjunct to more invasive tests to detect CRC and other causes of gastrointestinal (GI) bleeding.

CRC occurs most commonly in patients with a history of this type of cancer in a first-degree relative, adenomatous intestinal polyps, certain inherited genes, or inflammatory bowel disease. The incidence of CRC has been associated with advancing age, consumption of high amounts of red and processed meat, overweight/obesity, physical inactivity, smoking, and heavy alcohol use.³⁹

Usage Considerations

Two types of nonprescription FOBTs are available: pseudo-peroxidase-based toilet test (referred to as FOBT in the following discussion) and immunochemical-based FOBT (iFOBT), also referred to as the fecal immunochemical test. Both kinds of tests are noninvasive and easy to use in

the privacy of the home. A systematic review and meta-analysis of studies comparing guaiac-based FOBTs (gFOBT) with new-generation iFOBTs in CRC screening were performed. Data showed a statistically significant difference in the performance of gFOBT and iFOBT tests, with areas under the curve values of 0.77 and 0.87, respectively. Compared with the gFOBTs, the newer-generation iFOBTs were found to have a significantly higher diagnostic performance, suggesting that only fecal immunochemical tests should be used for CRC screening programs.⁴⁰

Accuracy Rate

The sensitivity and specificity values of FOBT for CRC detection obtained with guaiac tests (Hemocult cards) vary from 0.13 to 1 and from 0.69 to 0.99, respectively.⁴¹ The values for the iFOBT range from 0.42 to 0.94 and 0.4 to 1, respectively. FOBTs have better diagnostic performance for detecting distal colon cancer than proximal disease.⁴²

Mechanism of Action

Blood may be present on the surface of or contained within the stool matrix. In general, matrix blood originates in the upper GI tract, whereas surface blood comes from the lower tract. FOBT kits are more likely to detect blood from lower GI abnormalities. The FOBT toilet test detects blood in feces by a pseudoperoxidase reaction utilizing a chromogen that, when oxidized by hemoglobin, produces a blue-green color. The appearance of this color indicates a positive test.^{43,44} This type of kit is based on the premise that a significant amount of fecal blood from stool will remain on the surface of the toilet bowl water after a bowel movement.

The iFOBT uses antibodies to detect human hemoglobin protein in stool. This test reacts to heme, a part of the human hemoglobin protein, which is found in red blood cells; the test also is less likely to react to bleeding from parts of the upper digestive tract, such as the stomach. With this test, stool is sampled from toilet tissue after a bowel movement.

Interferences

In addition to cancer of the colon and rectum, blood in the stool can signify a number of conditions, including ulcers, Crohn's disease, colitis, anal fissures,

diverticulitis, and hemorrhoids. Any of these conditions can give a positive result to an FOBT.

Women who are menstruating should delay testing until menses has ceased. Menstrual blood that is present in the toilet bowl water or contaminates the stool sample can produce a positive result.

Aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and steroids may cause sufficient gastric bleeding to produce positive results. These medications ideally should be avoided for at least 2–3 days before testing and during the test period. However, available studies have not suggested a benefit in withholding these agents and have not directly assessed their impact on sensitivity or specificity.⁴⁵ Rectally administered medications also should be avoided.

False-Positive Guaiac FOBT

False-positive gFOBT results may be caused by the presence of animal-derived heme; consumption of large amounts of green vegetables that may have chlorophyll-mediated pseudoperoxidase activity; consumption of foods that have naturally high levels of peroxidase (e.g., broccoli, cauliflower, cantaloupe, carrots, squashes, figs, horseradish, grapefruit, melons, tomatoes, pumpkins, courgettes); or medications including NSAIDs, vitamin C, and iron. Chemical FOBTs could be positive if any bleeding is present in the GI tract. Of note, the diagnostic value of iFOBT is limited to the detection of bleeding from the lower GI tract because globin from the upper GI tract is readily degraded by digestive proteolytic enzymes.⁴⁶

The FOBT toilet tests are not specific for human blood and, theoretically, may produce false-positive results if red meat is consumed. However, a meta-analysis of dietary restriction studies found no difference in response rates between restricted and nonrestricted meat consumption before physician-based testing.⁴⁷ The manufacturer's instructions say no dietary restrictions are necessary.⁴³ Toilet bowl cleaners also may produce false-positive results in the toilet tests. The box "Patient Education for Fecal Occult Blood Tests" lists measures for avoiding inaccurate test results.

Usage Guidelines

See the box "Patient Education for Fecal Occult Blood Tests."

Patient Education for Fecal Occult Blood Tests

Toilet Test Products (EZ-Detect)

- Remove toilet tank cleansers or deodorizers, and flush toilet twice before testing.
- Keep test pads in original foil pouch until time of testing.
- Before testing, use one test pad to perform a water quality check. Hold the pad by its corners and drop it into the toilet bowl. If any trace of blue/green appears in the in the test area of the pad when the pad is placed in the toilet water, use another toilet to complete the testing. Perform this water quality check on the second toilet as well.
- Immediately after a bowel movement, place a pad in the toilet bowl, printed side up. After 2 minutes, check for the appearance of a color change (blue/green) on the test pad (positive result).
- If color changes differ from blue/green, discard the pad and repeat the test after the next bowel movement.
- Repeat the test on the next two bowel movements.
- If results are negative for all three tests, use remaining pad to perform a quality check of the test pads using the positive control chemical package that is provided. Flush the toilet and empty the contents of the package into the bowl as it refills. Float the remaining test pad in the water, printed side up. After 2 minutes, check for a blue/green color change, which indicates the test pads are working properly. If the color change does not appear, call the product manufacturer's assistance line provided with the product.

Source: EZDetect.com. ColoRectal Cancer Information Center: Screening Can Save Lives. Available at: <https://www.ezdetect.com/index.html>; accessed August 26, 2020.

Stool Application Product (Second Generation FIT)

- After a bowel movement, wipe the anal area as you normally do, and retain a small amount of stool on toilet paper.
- Unscrew cap/wand from buffer tube.

- Collect a small sample of stool onto the grooves of the buffer tube cap/wand.
- Return cap/wand to tube and screw tightly. Shake tube for 3 seconds. Unscrew smaller clear cap at top of tube.
- Apply 3 drops from tube to sample well.
- Read results after 5 minutes. There should be a red line at “C,” which indicates the test is working. A positive test also will have a line at “T.” Do not read results if 10 minutes has elapsed.

Source: Pinnacle BioLabs. Fecal Immunochemical Test. Available at: <https://www.pblabs.com/collections/fit-fecal-immunochemical-test>. Accessed August 26, 2020.

Avoidance of Incorrect Results

- Do not perform test during times of known bleeding, such as hemorrhoidal or menstrual bleeding.
- Increase dietary fiber intake for several days before testing. Roughage increases the accuracy of the test by stimulating bleeding from lesions that might not otherwise bleed.
- Because bleeding from cancerous lesions may be intermittent, perform the test on three consecutive bowel movements to increase the chance of detecting a possible lesion.
- Complete all three stool tests, even if the first two produce negative results.
- Do not take nonprescription medications such as aspirin and NSAIDs for 2–3 days before testing or during testing.
- Some prescription medications can cause bleeding and may need to be discontinued before testing. Consult a health care provider about which medications to stop taking before performing the test.

When to Seek Medical Attention

- Notify a health care provider if any of the tests are positive.

Product Selection Guidelines

All FOBT tests are similar in cost. Patients who do not want to use sample stool from toilet paper may wish to use the toilet test kits.

Assessment of Fecal Occult Blood Test Use

As with most health care scenarios that encompass many specialties, guidelines for colon cancer screening differ slightly between expert groups. For most patients, colon cancer screening should start at 50 years of age and be conducted every 5–10 years. Key stakeholders have made the recommendations in the following sections.

The U.S. Preventive Services Task Force recommends the use of FOBT, sigmoidoscopy, or colonoscopy for screening. This group recommends that adults ages 50–75 years be screened for CRC. The decision to be screened after age 75 should be made on an individual basis.⁴⁸ Because of better sensitivity, the American College of Gastroenterology recommends that colonoscopy rather than FOBT be used to screen for colon cancer.⁴⁹

The American Cancer Society's screening guidelines recommend that people at average risk of CRC start regular screening at age 45 years. People who are in good health and with a life expectancy of >10 years should continue regular CRC screening through the age of 75. People at increased or high risk of CRC, as defined in the guidelines, might need to start screening before age 45, be screened more often, and/or undergo specific tests.⁵⁰ Other screening guidelines have similar recommendations.⁵¹

For those at increased risk for colon cancer, FOBT is not recommended. Patients seeking information about FOBT should be assessed for risk factors for colon cancer. Those with risk factors should be encouraged to have a screening test other than FOBT. Determining the potential for false test results is an important consideration. False-negative tests could delay necessary treatment, whereas false-positive tests could cause unwarranted anxiety and expensive follow-up testing.

Patient Counseling for Fecal Occult Blood Tests

When counseling a patient on the use of FOBTs, the health care provider

should emphasize the importance of following package instructions carefully. The box “Patient Education for Fecal Occult Blood Tests” lists specific information to provide patients.

Evaluation of Patient Outcomes With Fecal Occult Blood Tests

A patient evaluating the results of an FOBT must remember that the test is a screening method and is not specific to a particular disease. A positive test result may indicate any medical condition that causes a loss of blood through the GI system. The primary value of FOBT is to alert patients and their providers that a thorough workup may be needed. The kits are not intended to replace other diagnostic procedures. Patients should be advised to contact their provider if a positive test result is obtained.

Cholesterol Tests

Elevated levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides, along with low levels of high-density lipoprotein cholesterol (HDL-C), are major contributors to the development of atherosclerotic heart disease, which can result in heart attack and stroke. Data from the Centers for Disease Control and Prevention (CDC) suggest that high cholesterol continues to be a concern for a significant number of Americans⁵²:

- In 2015–2016, more than 12% of American adults ages 20 years or older had total cholesterol (TC) levels >240 mg/dL, and more than 18% had high-density lipoprotein (HDL, or “good”) cholesterol levels <40 mg/dL.
- Of U.S. adults ages 20 years or older, 95 million have total cholesterol levels >200 mg/dL. Nearly 29 million adult Americans have total cholesterol levels >240 mg/dL.
- Of U.S. children and adolescents ages 6–19 years, 7% have high total cholesterol.⁵²

A multi-organizational task force suggests that most healthy adults should have their cholesterol checked every 4–6 years. Those who have heart disease, diabetes, or a family history of high cholesterol should be tested more frequently. Children and adolescents should have their cholesterol checked at

least once between ages 9 and 11 years and again between ages 17 and 21.^{53,54}

A home cholesterol test is one means of achieving this critical step to minimize the risk for cardiovascular disease. However, this test should not replace a complete lipid panel conducted by a health care provider. Because elevated cholesterol is a chronic condition that requires lifestyle modification and, frequently, medication for treatment, adhering to a treatment plan can be difficult for patients. Home cholesterol tests can help them monitor the efficacy of and adherence to diet, exercise, and medication plans.

Usage Considerations

Some nonprescription cholesterol tests measure only total cholesterol, whereas others also measure LDL-C, HDL-C, and triglyceride levels (Table 48–5).^{55–61} Individuals with diabetes might want to consider a device that measures glucose levels in addition to cholesterol and triglyceride levels. The kits CardioChek Plus Analyzer,⁵⁵ Mission Cholesterol Monitoring System,⁶¹ Curo L5 Cholesterol Test Kit,⁵⁹ and First Check Cholesterol Home Test⁵⁶ allow patients to measure their total blood cholesterol levels at home. The Check Up America,⁶⁰ LetsGetChecked,⁵⁷ and the EverlyWell⁵⁸ tests offer a self-collected, laboratory-performed test for a complete lipid profile.

TABLE 48–5 Selected Nonprescription Cholesterol Tests and Features	
Trade Name (Website)	Product Features
CardioCheck ⁵⁵ (ptsdiagnostics.com/ cardiochek-home-use-analyzer/)	• Fingerstick blood sample collection • Portable, palm-sized • Large digital readout • Accuracy relied upon by health/wellness programs and physicians • Provides TC, HDL cholesterol, TG, and blood glucose levels in ≤90 seconds; provides estimated LDL level • Can be programmed to display in nine languages: English, Spanish, German, French, Italian, Portuguese, Dutch, Chinese, and Russian (not all languages are available in all locations) • Blood sample placed on test strip; analyzer uses reflectance photometry to read color changes
First Check Cholesterol Home Test ⁵⁶	• Total cholesterol and HDL values provided; estimated LDL value

Trade Name (Website)	Product Features
	provided • Fingerstick blood sample collection • Results provided in 5 minutes • Fasting before testing not required • Test available only through third-party retailers • Whole blood sample is applied to receiving pad on reverse side of test strip. Blood sample is absorbed and reacts with reagents found on front side of test strip, producing a color that is compared with the supplied color chart to identify TC or HDL level in sample (Dixita Amin, Technical Support Associate, Abbott Rapid Diagnostics, San Diego, California, personal communication, August 12, 2020).
Curo L5 – Cholesterol Test Kit – At Home Blood Testing Meter & Strips⁵⁹ (www.curofit.com/s/blood-cholesterol/)	• Fingerstick blood sample collection • Measures via enzyme chromophoric spectroscopy • Capable of screening lipid profile, including LDL, HDL, TC, TG levels • Specific strips required for more-comprehensive test results • Results available in <2 minutes • Instant auto-coding with RFID chip recognition. • User-selectable, average measurement range (customizable ≤99 days) • PC/printer connection port for easy data transfer
EveryWell Cholesterol and Lipids Test⁵⁸ (www.everlywell.com/products/cholesterol-and-lipids-test/)	• Fingerstick blood sample collection • Sample sent to and analyzed in CLIA-certified laboratory • TC, HDL, TG, and calculated LDL levels • Independent board-certified physician reviews results • Results provided via secure platform within days
CheckUp America Cholesterol Panel⁶⁰ (www.homeaccess.com/product/checkup-america-cholesterol-panel/)	• FDA-approved mail-in test • Fingerstick blood sample collection • Tests done in CLIA-approved laboratory • TC, HDL, TG, calculated LDL levels provided • Results provided 5 days after sample receipt via USPS or manufacturer's secure website • Counseling and assistance available via phone

Key: CLIA = Clinical Laboratory Improvement Act; FDA = U.S. Food and Drug Administration; HDL = high-density lipoprotein; LDL = low-density lipoprotein; RFID = radio-frequency identification; TC = total cholesterol; TG = total triglyceride; USPS = U.S. Postal Service.

Mechanism of Action

CardioChek and the Mission Cholesterol Monitoring System use a reflectance photometer to read the color intensity of the chemical test reaction on the test strip.^{55,61} The Curo L5 Cholesterol Test Kit uses enzyme chromophoric spectroscopy⁵⁹; as with a glucose meter, test results are displayed on a screen. The First Check Cholesterol Home Test includes test strips that are treated with chemical reagents. A whole blood sample is absorbed on a receiving pad on the back of a test strip. The blood sample absorbs through to the front of a test strip and reacts with the reagents. The reaction area produces a color that can be compared with a supplied color chart for TC or HDL concentrations.⁵⁶ LetsGetChecked, EverlyWell, and Check Up America's lipid profile tests are performed by a CLIA-certified laboratory.^{57,58,60}

Accuracy Rate

The accuracy rate of home cholesterol tests is debated. Except for the tests that are mailed to a laboratory, the remaining products described here are FDA approved for home use, are CLIA-waived devices, and are rated substantially equivalent to a laboratory-based cholesterol test. Health care providers should emphasize to patients the importance of following a specific test's directions to ensure accurate results.

Interferences

Good fingerstick technique is necessary to avoid erroneous results from cholesterol tests. Two or three hanging drops of blood are needed, but excessive squeezing and milking of the finger will negatively affect the quality of the blood sample. If sufficient blood cannot be obtained from the first fingerstick, the patient should use a different finger. A low cholesterol value may result if the blood sample is too small or if it takes >5 minutes to collect the necessary amount of blood.

The patient should avoid doses of ≥ 500 mg of vitamin C before the test to avoid obtaining an artificially low result. Vitamin C slows the development of the color reaction by slowing the rate at which peroxide is produced and has been shown to interfere with all home-based tests.

Usage Guidelines

See the box “Patient Education for Cholesterol Tests.”

Patient Education for Cholesterol Tests

Usage Guidelines

- Before starting the test, wash your hands thoroughly with soap and warm water, and then dry them.
- To stabilize the cholesterol level, sit and relax for 5 minutes before performing the test.
- CardioChek Test: Insert the memory chip corresponding to the desired test into the meter; then turn on the meter.
- To obtain the blood sample, use the provided lancet to lance the outside of one fingertip, and wipe away the first drop of blood with the provided gauze pad, wipe, or tissue.
- Apply blood to the test strip or pad as quickly as possible. For cholesterol meters, apply enough blood to cover the testing area of a strip.
- Cholesterol meter: A test strip may need to be inserted before applying blood for the meter to read the bar code. The test strip can be removed to apply the blood sample. The meter displays the test results in approximately 1–5 minutes.
- For kits that require a sample test be sent to a laboratory, be sure to follow the detailed instructions to register your kit, collect the blood sample properly, and mail it to the laboratory. Each manufacturer has a detailed video explaining these processes.

Avoidance of Incorrect Results

- If two or three hanging drops of blood cannot be obtained, or if it

takes longer than 5 minutes to collect this amount of blood, do not perform the test.

- Do not excessively squeeze or milk the finger.
- If taking vitamin C in doses of ≥ 500 mg, do not take the dose within 4 hours of testing.
- The lancet is a biohazard; dispose of it in a puncture-resistant container.

When to Seek Medical Attention

- If the total cholesterol reading is ≥ 200 mg/dL, HDL-C is ≤ 40 mg/dL, or triglycerides are ≥ 150 mg/dL, see a health care provider for evaluation and further testing.

Key: HDL-C = High-density lipoprotein cholesterol.

Product Selection Guidelines

Although significantly more expensive than individual total cholesterol test cassette kits, the cholesterol meters are reusable with the purchase of additional testing materials and will store test results. Some of the meters have the ability to test for HDL-C and triglycerides, whereas the other home tests measure only TC. Some companies provide a lipid profile performed in a CLIA-certified laboratory, but the results are not immediately available.

Assessment of Cholesterol Test Use

Whether the patient has been diagnosed with or has some reason to be concerned about hypercholesterolemia should be determined before a cholesterol test is recommended. Any factors that could affect the test results also should be determined.

Patient Counseling for Cholesterol Tests

Counseling about cholesterol tests should emphasize the importance of properly collecting blood samples. If needed, patients should be advised to seek assistance with the fingerstick. As further assurance of accurate test

results, patients should be advised of factors that can cause inaccurate test results. The box “Patient Education for Cholesterol Tests” lists specific information to provide patients.

Evaluation of Patient Outcomes With Cholesterol Tests

Any patient who obtains a total cholesterol result of ≥ 200 mg/dL, an HDL-C ≤ 40 mg/dL, or triglycerides ≥ 150 mg/dL should see a health care provider for a full lipid profile and appropriate medical workup. Patients should not adjust their cholesterol-lowering medications based on results of a home test without consulting their provider.

Urinary Tract Infection Tests

Urinary tract infections (UTIs) are the most common outpatient infections in the United States, resulting in more than 8.5 million health care visits and accounting for more than \$1.6 billion in health care expenses. Although diagnostic symptoms such as change in frequency, urgency, dysuria, and blood in the urine may suggest a UTI, elderly women may present with all, some, or none of these symptoms. In those with a high probability of infection, a negative test result should not be considered confirmatory, and subsequent assessment is warranted. Urine culture remains the gold standard for diagnosing a UTI.⁶²

The prevalence of UTIs is much greater in women than in men and typically increases with age, although women ages 14–24 years also have a high incidence. The overall incidence in adult women is approximately 11%, whereas the incidence in women ages 65 years or older is roughly 20%. More than half of all adult women will have at least one UTI in their lifetime. The most common pathogens for uncomplicated UTIs include UroPathogenic *Escherichia coli* (UPEC) (75%), *Klebsiella pneumonia* (6%), and others collectively (19%).⁶³

Women have a shorter urethra compared with men and therefore are more likely to contract UTIs because of retrograde migration of bacteria from the skin. Conditions that increase risk of UTIs include pregnancy, diabetes, urinary

stones, urinary obstructions such as those caused by an enlarged prostate, presence of urinary catheters, and a history of UTIs.⁶⁴

Two primary uses for UTI tests are (1) early detection of an infection in patients with a history of recurrent UTIs or risk factors associated with UTIs and (2) confirmation that an infection has been cured by antibiotic therapy.

Usage Considerations

A number of home UTI tests are available, and all involve the use of a test strip and a patient's urine sample. The primary difference is whether the strip is used "midstream" or dipped in a urine collection cup.

Mechanism of Action

The EasyHome Urinary Tract Infection test strips, AZO test strips, and store-brand strips detect both nitrite and leukocyte esterase (LE), an enzyme unique to *leukocytes* (white blood cells).^{65,66} White blood cells may be found in the urine when a UTI is present. Gram-negative bacteria reduce nitrate in the urine to nitrite. Arsanilic acid in the test strip reacts with urinary nitrite to form a diazonium compound, which in turn reacts with another chemical on the strip to produce a pink color. A positive test requires a bacterial concentration of 10^5 per milliliter of urine. LE detection helps identify infections with gram-positive organisms that would be missed with testing for only nitrites.

Accuracy Rate

Combining nitrite and LE in one test increases overall sensitivity compared with either alone.

A study assessing the sensitivity of dipstick testing for nitrites, LE, and blood in 635 culture-positive patients showed poor predictability. The least sensitive test was nitrite (23.3%), followed by LE (48.5%), and blood (63.9%); combining all three parameters in one test provided 74% sensitivity.⁶⁷

Another study found testing for nitrite and LE provided more sensitive and predictive results. Nitrite has the best sensitivity (95%), followed by LE (73%); predictive values for each were 84% and 51%, respectively. Interestingly, a combination of clinical symptoms (fever, lower abdominal pain, and dysuria)

had a 92% specificity.⁶⁸

Interferences

A strict vegetarian diet that provides insufficient urinary nitrates can cause false-negative nitrite results for a UTI test. Tetracycline and vitamin C in excess of 250 mg also may produce a false-negative reading for nitrites by blocking the nitrite test reaction. Doses of vitamin C in excess of 500 mg within 24 hours of testing may result in a false-negative result for the LE test by blocking the development of the color reaction.⁶⁹ The patient should allow 10 hours between the last dose of vitamin C and the test procedure. Dyes or medications such as phenazopyridine, occasionally used by patients with UTIs, may cause a false-positive result by changing the sensor pad to pink.

Usage Guidelines

See the box “Patient Education for Urinary Tract Infection Tests.”

Patient Education for Urinary Tract Infection Tests

Usage Guidelines

- Clean the genital area thoroughly before collecting a urine sample.
- Test the first urine of the morning or, for later testing, use urine held in the bladder for at least 4 hours.
- To improve sensitivity, test on 3 consecutive days if the test on the previous day was negative.
- Pass the test strip through the urine stream, or immerse sensor pad for 1–2 seconds in urine collected in a clean cup.
- Do not touch the sensor pad with your fingers because skin oils can interfere with the test reaction.
- Make sure urine completely covers the pad.
- Most tests provide results for 2 chemicals that indicate a possible infection: leukocytes and nitrites.
- Wait the indicated time (1–2 minutes to account for testing for both chemicals); then compare the color on the sensor pad with the color chart provided.

- Wait no longer than 3 minutes to read the test strip, and ignore any color changes that occur after that time.

Avoidance of Incorrect Results

- Persons on a strict vegetarian diet or tetracycline may not obtain accurate results.
- Certain dyes or medications, such as phenazopyridine, may cause a false-positive result by changing the sensor pad to pink.
- Do not take 250 mg or more of vitamin C within 24 hours of testing; this may cause a false-negative result.
- Women should not use the test during menses because menstrual blood will cause a false-positive result.

When to Seek Medical Attention

- Contact a health care provider immediately for evaluation and treatment of any positive test.
- If the test is negative but symptoms persist, see a health care provider immediately for evaluation and treatment.

Product Selection Guidelines

UTI tests have small test strips. The EasyHome Urinary Tract Infection Test Strips can be used midstream or after urine is collected in a cup. The AZO test strips have a small, attached handle that may make it easy to hold the strip in the urine stream. Some patients will prefer one option over the other, so it is important that they know both options are available.

Assessment of Urinary Tract Infection Tests

The patient's reason for using a UTI test should be determined before a test is recommended. If the patient is testing for a suspected UTI, the patient's symptoms and risk factors for UTIs should be evaluated. If symptoms of a UTI are present, the patient should be referred to his or her health care provider immediately for evaluation and treatment. If the patient is testing to find out

whether a treated UTI has been cured, the patient's adherence to the therapy should be assessed. The patient's diet and medication use are important factors to evaluate for possible interference with test results.

Patient Counseling for Urinary Tract Infection Tests

If the sensor pad is to be immersed in a cup of urine, counseling on the use of UTI tests should emphasize the importance of collecting a clean sample of midstream urine in the provided cup or in a clean, unwaxed container. A patient with visual difficulties should be advised to seek assistance in interpreting test results. As further assurance of accurate test results, patients should be advised of medical and dietary factors that can cause inaccurate test results. The box "Patient Education for Urinary Tract Infection Tests" lists specific information to provide patients.

Evaluation of Patient Outcomes With Urinary Tract Infection Tests

Because UTI tests will detect only about 90% of infections, the patient should contact a health care provider if a negative result is obtained but UTI symptoms persist. If the result is positive, the patient should contact a health care provider immediately for evaluation and treatment.

Human Immunodeficiency Virus Tests

In 2016, the WHO published the first global guidelines on HIV self-testing. The guidelines recommend that HIV self-testing be offered as an additional approach to HIV testing services.⁷⁰ Data from 2018 in the United States show that approximately 1.2 million people were living with HIV, with just over 36,000 new cases that year. It is estimated that 14% (1 in 7) of persons with HIV do not know they are infected and need testing. HIV continues to have a disproportionate impact on certain populations, particularly racial and ethnic minorities and gay and bisexual men. Although annual infections have been

reduced by more than two-thirds since the height of the epidemic in the mid-1980s, CDC data indicate that progress has stalled in recent years. Home HIV tests allow a person to test in privacy.⁷¹

Acquired immunodeficiency syndrome (AIDS), an incurable disease caused by HIV infection, destroys the body’s immune system. HIV infection can be contracted by contact with infected body fluids such as blood or semen. People at risk for contracting the virus include those who (1) share needles or syringes for the purpose of injecting drugs, including steroids; (2) have sexual intercourse with a person infected with HIV, with someone who injects drugs, or with multiple partners; (3) had a blood transfusion anytime between 1978 and May 1985; and (4) were born to a mother infected with HIV.

Usage Considerations

Home test kits that require saliva or blood samples for HIV detection are currently available (Table 48–6). Kits that use a blood sample require the sample to be mailed off for testing. In contrast, OraQuick, a saliva-based kit, provides a result in approximately 20 minutes.

TABLE 48–6 Selected Nonprescription HIV Tests and Features	
Trade Name (Information Source)	Product Features
Let’s Get Checked Home STD Test Kit (www.letsgetchecked.com/us/en/home-std-test/)	• Tests for presence of antibodies to HIV-1, HIV-2, and P24 antigen • Test activation required online • Morning fingerstick blood sample collection recommended • Sample sent to company for analysis in CLIA-certified laboratory • Online results obtained 2–5 days after sample received • Medical experts contact user to explain results and provide treatment options
NURX Sexually Transmitted Infection (STI) Home Test Kit (www.nurx.com/sti-testing/)	• Offers multiple test kits,

Trade Name (Information Source)	Product Features
	including HIV (type not specified) testing • User downloads NURX app or visits website • User answers questions about health history, and then selects appropriate STI test kit • Data reviewed by NURX medical provider team to help determine appropriate test kit • After review, test shipped to patient • For HIV, fingerstick blood sample applied to blood spot card • Mailed blood sample analyzed in CLIA-certified laboratory • Within 7 days, NURX medical team contacts patient to discuss results • NURX experts can prescribe therapy, if needed
Everlywell HIV Test (www.everlywell.com/products/hiv-test/)	• Tests for presence of antibodies to HIV 1 and 2 • Each kit has unique ID to allow user to register kit and establish account where confidential results will be posted • Fingerstick blood sample collection • Sample returned to company for analysis in CLIA-certified laboratory • Results reviewed by independent board-certified physician • Data posted within days on manufacturer's secure platform
myLabBox HIV Home Test Kit (www.mylabbox.com/product/hiv-home-test-kit/)	• Mail-in kit tests for HIV-1 and

Trade Name (Information Source)	Product Features
	HIV-2 • Combo antigen/antibody ELISA for qualitative detection of HIV p24 antigen and antibodies to HIV-1 groups M and O and HIV-2 in human blood. • Fingerstick blood sample collection • Test conducted in CLIA-certified laboratory • Results received in 2-5 days • FDA-approved technology • Free telemedicine physician consultations for those who test positive • >99.9% accuracy rate
Health Testing Centers Complete STD Test Kit (HIV; type not specified) and Total STD Test Kit (HIV; type not specified); HIV Test Kit (HIV-1, HIV-2, p24 antigen) (www.healthtestingcenters.com/std-testing/)	• Fingerstick blood sample collected • Sample mailed to CLIA-certified laboratory • Results provided in 3-4 business days • Medical provider consultation available for those who test positive
OraQuick: In-Home HIV Test (www.oraquick.com/)	• Oral swab of upper and lower gums required • Swab inserted into provided test tube, where sample fluid mixes with liquid reagent; mixture migrates up test stick • Results (positive or negative for antibodies) available in 20 minutes • HIV infection unlikely if negative result is obtained, at least 3 months has passed since the risk event, and patient followed test directions carefully

Trade Name (Information Source)	Product Features
	• Regular testing recommended if negative test result obtained but patient engages in high-risk activities for HIV infection • For positive results, discussion of results and options with health care provider recommended • Website links provided to locate health care professionals, clinics, local health departments, and other resources based on geographic location

Key: CLIA = Clinical Laboratory Improvement Act; ELISA = enzyme-linked immunosorbent assay; FDA = U.S. Food and Drug Administration; HIV-1 = human immunodeficiency virus type 1; HIV-2 = human immunodeficiency virus type 2; STD = sexually transmitted disease; STI = sexually transmitted infection.

Mechanism of Action

The HIV tests detect antibodies to the virus. Because 3 weeks to 6 months may be required for an exposed individual to develop sufficient antibodies for detection, the time of possible exposure to the virus must be considered in determining when to perform the test.

The saliva test detects antibodies to both HIV-1 and HIV-2 using technology similar to that used in home pregnancy tests.⁷² Through a lateral flow process, the saliva specimen is wicked up by the device; HIV antibodies, if present, bind to the colloidal gold particles. The bound HIV antibodies then bind to an HIV antigen “T” line, forming a visible red band.

After collection, the home HIV test blood samples are mailed to a certified laboratory for processing. Positive samples are rescreened twice. Repeated positive samples are confirmed with an immunofluorescent assay.⁷³

Interferences

Providing an inadequate blood sample (i.e., incompletely filling the circle on the blood sample card) or inadequately swabbing the gums to provide an adequate saliva sample may cause inaccurate results. Patients taking immunosuppressant therapy may not be able to produce sufficient levels of antibodies and may obtain a false-negative result.

Usage Guidelines

See the box “Patient Education for HIV Tests.”

Patient Education for HIV Tests

Usage Guidelines—Blood Tests

- Call the product manufacturer’s toll-free number to register and receive pretest counseling. The manufacturer’s customer representative will ask for the confidential code included in the kit. Some test kits can be obtained and registered online.
- Once you have the kit, review the detailed instructions before beginning the sample collection process.
- Using the alcohol swab provided, clean the fingertip chosen for puncture. Allow alcohol to dry.
- Prick the cleaned fingertip using the lancet provided.
- Wipe away the first drop of blood with the provided gauze or tissue.
- Collect the blood sample in the provided collection device. This device may be a tube or a card. If a card is supplied, examine the back of the card to ensure that the blood soaked through. If not, place more blood on the front of the card. If a second fingerstick is needed, use the second lancet provided in the kit.
- Manufacturers have videos on their websites that illustrate exactly how samples should be collected.
- For cards, allow blood sample to air dry for 30 minutes, place the sample in the specimen return pouch; and seal the pouch in the prepaid and addressed shipping package. Be sure that the processing laboratory receives the specimen within 10 days of

sampling.

- To obtain the results, call the manufacturer's toll-free number 3–7 business days after mailing the specimen, depending on which test kit was used. Many companies also have secure websites where results can be obtained via a secure login.
- Note that counseling is available 24 hours a day, for both negative and positive results, and counseling is included in the cost of the testing unit.

Precautions—Blood Tests

- Do not share the test lancet with other individuals. Do not allow the blood being tested to contact other individuals.
- The lancet is a biohazard; dispose of it in a puncture-resistant container.

Usage Guidelines—Saliva Tests

- A timer or watch is needed.
- Remove the test tube from packaging, keeping it upright because it contains liquid that must not be spilled.
- Pop the top of the tube off, and insert it into the holder located inside the lid of the packaging.
- Remove the test stick from packaging. Do not touch the test pad.
- Swipe the test pad along upper and lower gums. Swipe each gum only once.
- Insert the test stick into the test tube with the test window facing forward. Start timing.
- Read the test result in the test window at 20 minutes. After 40 minutes, the results may be invalid.
- The test kit provides guidelines for how to read the results and what the results mean. The appearance of a line at C is a negative result. A line appearing at C and T is a positive result.
- Note that counseling on performing the test is available 24 hours a day from the company.

Avoidance of Incorrect Results—Saliva Test

- Do not open any of the packets until you are ready to begin the test.
- Do not eat, drink, or use oral care products (such as mouthwash, toothpaste, or whitening strips) for 30 minutes before starting the test.
- Remove dental products such as dentures or retainers that cover gums.
- To prevent a false-positive result, swab each gum only once.

When to Seek Medical Attention

- If the test is positive, see a health care provider immediately for evaluation and treatment. Avoid activities that can result in transfer of blood or other body fluids to other individuals.

Product Selection Guidelines

Many people will prefer to use the saliva test because it gives faster results, does not require a fingerstick, and has a price similar to that of some of the other mail-in tests. The two available HIV blood tests differ in price and turnaround time to obtain results. Most manufacturers provide results in 2–7 days and have physicians on staff to interpret the results, and if requested, to provide a consultation.

Assessment of HIV Test Use

The elapsed time since possible exposure to the HIV virus should be determined before an HIV test is recommended. The patient may not know all the risk factors for HIV infection; therefore, whether the patient has engaged in any activities that increase risk for contracting HIV should be determined tactfully. The patient should be asked about medical disorders that might rule out the use of a fingerstick-based test, such as use of an anticoagulant or antiplatelet agent, presence of a bleeding disorder, or physical limitations that might interfere with performing the test.

Patient Counseling for HIV Tests

Counseling on the use of HIV blood tests should emphasize the importance of

applying enough blood on the specimen card to ensure an accurate reading. Patients also should be advised of the fragility of blood samples and not to delay mailing the specimen card. Counseling for the saliva test should emphasize the importance of adequately swabbing the gums with the test stick. The box “Patient Education for HIV Tests” lists specific information to provide patients.

Evaluation of Patient Outcomes With HIV Tests

A patient with a positive result should see a health care provider to be retested for confirmation of HIV infection. Infected patients should be counseled on precautions to avoid infecting others. Patients with negative results should confirm that sufficient time has passed since the potential exposure.

Hepatitis C Tests

Hepatitis C is one of six identified hepatitis viruses. Hepatitis C is the most commonly reported bloodborne infection in the United States. Surveys conducted during 2013–2016 indicated an estimated 2.4 million persons were living with hepatitis C. The CDC recommends that the following groups be tested for hepatitis C⁷⁴:

- Patients ages 18 years or older
- Pregnant patients
- Current and former IV drug users
- HIV-positive patients
- Patients with abnormal liver tests or liver disease
- Patients on hemodialysis
- Patients who received donated blood or organs before July 1992
- Patients who received clotting factor concentrates before 1987
- Patients who have been exposed to blood from a person who has hepatitis C
- Patients who were born to a mother with hepatitis C

FDA provides consumer information about the home test, high-risk groups, the value of testing, and actions to take after the results are obtained.⁷⁵

Hepatitis C induces liver damage by causing hepatic cell necrosis and

inflammation, which over time may progress to fibrosis, cirrhosis, and hepatocellular carcinoma. Of people infected with hepatitis C, a significant number are likely to progress to the chronic disease state. Clinically, hepatitis C may go undetected for many years, and liver disease may be advanced by the time symptoms arise. This is one reason why the groups recommended for testing have expanded over the last several years.

Usage Considerations

Each of the available kits (Table 48–7) provide the necessary supplies for obtaining a sample that is mailed to a CLIA-certified laboratory for analysis. Results are typically available 2–7 days after the sample is received at the laboratory. Most manufacturers have medical experts that review the results and provide guidance on treatment options and the next steps to take.

TABLE 48–7 Selected Nonprescription Hepatitis C Tests and Features

Trade Name (Website)	Product Features
myLAB Box Hepatitis C Home Test Kit (www.mylabbox.com/product/hepatitis-c-home-test/)	• Fingerstick blood sample is collected. • Sample is mailed to laboratory. • Results are available in 2–5 days. • Sample is analyzed by CLIA-regulated clinical laboratory affiliates. • Free telemedicine physician consultations are available for those who test positive. • Test is >99.9% accurate and is as reliable as tests used by physicians and hospitals.
Let's Get Checked Home Hepatitis C test kits (www.letsgetchecked.com/us/en/home-hepatitis-c-test/)	• Tests are available for hepatitis C only and for hepatitis B and C. • Online test activation is required. • Fingerstick blood sample should be collected in the morning. • Sample is returned to company. • Sample is analyzed in CLIA-certified laboratory. • Online results are available within 2–5 days of receipt of sample. • Medical experts are available to contact

Trade Name (Website)	Product Features
	user to explain results and provide treatment options.
Everlywell Hepatitis C Test (www.everlywell.com/products/hepatitis-c-test/)	• Unique ID for each kit allows user to register kit and establish account for confidential posting of results. • Fingerstick blood sample is collected. • Sample is analyzed in a CLIA-certified laboratory. • Test results are reviewed by an independent board-certified physician. • Data are posted on company's secure platform within days.
NURX Sexually Transmitted Infection (STI) Home Test Kit (www.nurx.com/sti-testing/)	• Multiple test kits are offered: Full Control Test Kit includes hepatitis C testing. • Users download Nurx app or visit Nurx website. • Users answer questions about health history and select home STI test kit of interest. • NURX medical provider team reviews data and helps determine best test kit option. • Test kit is shipped after purchase is finalized. • For Hep C test, fingerstick blood sample is applied to blood spot card. • Sample is mailed to NURX and analyzed in CLIA-certified laboratory. • Within 7 days, NURX medical team contacts patient to discuss results. • NURX experts can prescribe therapy, if needed.
Health Testing Centers STD test kits (www.healthtestingcenters.com/std-testing/)	• Company offers multiple test kits that include an option to test for hepatitis C. • Fingerstick blood sample is collected. • Results are available in 3-4 business days. • Tests are performed in CLIA-certified

Trade Name (Website)	Product Features
	laboratory. • Users who test positive can discuss treatment options with a medical provider.

Mechanism of Action

The available kits test for presence of antibodies to the hepatitis C virus (HCV), not the virus itself. The HCV antibody test is used for initial screening for hepatitis C. The test is performed by enzyme immunoassays (EIAs), which detect the presence of hepatitis C antibodies in serum. The test result is reported as positive or negative. Third-generation EIAs have a sensitivity/specificity of approximately 99%. However, the presence of HCV antibodies does not indicate whether the infection is acute, chronic, or resolved. A positive antibody test result should be followed up with an HCV RNA test to confirm that viremia is present.⁷⁶ Because 6 months may be required to develop sufficient antibodies for detection, the time since possible exposure to the virus must be considered in determining when to perform the test.

Interferences

Providing an inadequate blood sample (i.e., incompletely filling the circle on the blood sample card) may cause inaccurate results. Patients taking immunosuppressant therapy may not be able to produce sufficient levels of antibodies and, therefore, may obtain a false-negative result.

Usage Guidelines

See the box “Patient Education for Hepatitis C Tests.”

Patient Education for Hepatitis C Tests

Precautions

- Do not share the test lancet with other individuals.

- Do not allow the blood being tested to contact other individuals.
- The lancet is considered a biohazard; dispose of it in a puncture-resistant container.

Usage Guidelines

- Register the PIN (personal identification number) with the manufacturer by calling the provided toll-free telephone number and following the automated directions. Some manufacturers allow for secure online registration.
- Remain seated during the testing process to prevent falling if dizziness occurs.
- Date the blood sample card.
- Before starting the test, wash your hands thoroughly with soap and warm water, and then dry them.
- Prick the cleaned fingertip using the lancet provided.
- Wipe away the first drop of blood with the provided gauze or tissue.
- Collect the blood sample in the provided collection device. This may be a tube or a card. If a card is supplied, examine the back of the card to ensure that the blood soaked through. If not, place more blood on the front of the card. If a second fingerstick is needed, use the second lancet provided in the kit.
- Manufacturers have videos on their websites that illustrate exactly how samples should be collected.
- Allow cards to air dry for 30 minutes; place the sample in the specimen return pouch; and seal the pouch in the prepaid and addressed shipping package.
- Within 4–10 business days after mailing the sample, call the toll-free number provided or log into the secure portal, using your personalized PIN, to access your test results.
- Note that counseling is included in the cost of the testing unit and is available 24 hours a day, for both negative and positive results.

When to Seek Medical Attention

- If the test is positive, see a health care provider immediately for evaluation and treatment. Avoid activities that can result in transfer

of blood or other body fluids to other individuals.

Product Selection Guidelines

Multiple hepatitis C test kits are available ([Table 48–7](#)). They have similar processes for sample collection and testing.

Assessment of Hepatitis C Test Use: A Case-Based Approach

A patient who has been infected recently may receive a false-negative result because antibodies to the virus have not had sufficient time to form. Clinical studies on file with the manufacturer of Hepatitis C Check report no false-positive results.⁷⁷ The patient may not know all the risk factors for hepatitis C; therefore, whether the patient has engaged in any activities that can cause the disease should be determined tactfully. The patient should be asked about medical disorders that might rule out use of a fingerstick-based test or physical limitations that could interfere with performing the test. Case 48–2 is an example of assessment of a patient who wishes to test for hepatitis C infection.

Patient Counseling for Hepatitis C Tests

Patients should be advised of the fragility of blood samples and not to delay mailing the specimen card. The box “Patient Education for Hepatitis C Tests” lists specific information to provide patients.

Evaluation of Patient Outcomes With Hepatitis C Tests

Patients who test positive should be referred to a health care provider because treatment options are available only by prescription. Infected patients should be counseled on precautions to avoid infection of others. These patients also should be advised to avoid using alcohol and other drugs that may advance the progression of liver disease. Finally, they should be tested for and

vaccinated against other forms of hepatitis, such as the hepatitis A and B viruses.

Case 48–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient recently read an article about the high rate of hepatitis C infections in Baby Boomers.
b. Medical history, including family history	He has heart disease, high cholesterol, GERD, rheumatoid arthritis, and hypertension. He did have a blood transfusion years ago but is evasive when asked about other risk factors.
c. Patient's identity	Jose Martinez
d. Patient's age, gender, height, and weight	64 years old, male, 5 ft 9 in., 191 lb
e. Patient's dietary habits	n/a
f. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Atorvastatin 20 mg, lisinopril 10 mg, pantoprazole 40 mg, Xeljanz XR 11 mg, and an eye vitamin, all once daily; methotrexate 7.5 mg once weekly. Adherence to medications verified by refill records. Just completed a 7 day course of prednisone.
g. Prior use of diagnostic/monitoring test	Jose has never used any home tests.
h. Potential problems with performing/interpreting test	He wears reading glasses to read fine print. His wife could help him read the instructions and complete the test.
Assess	

Relevant Evaluation Criteria	Scenario/Model Outcome
2. Determine whether self-testing is appropriate.	Although he should be screened for hepatitis C because of his age group, self-testing is not appropriate.
3. Identify exclusions for self-treatment.	Immunosuppressant therapy and unknown immune system status
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a medical provider is required, and share this information with the patient or caregiver.	Options include (1) Refer patient for hepatitis C testing. (2) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	The patient understands why self-testing is not appropriate. He has an appointment with his HCP in 3 weeks and will ask for the test at that time.
Follow-up: Monitor and Evaluate	
6. Assess patient outcome.	Pharmacist will check with the patient at his next pharmacy visit to see if the test was performed or is scheduled.

Key: HCP = Health care provider; GERD = gastroesophageal reflux disease; n/a = not applicable.

Drug Abuse Tests

Data from the 2017 National Survey on Drug Use and Health (NSDUH)⁷⁸ show that

- 30.5 million people ages 12 years or older had used an illicit drug in the past 30 days (i.e., current use), which corresponds to about one in nine

or 11.2% of Americans.

- About one in four young adults ages 18 to 25 were current illicit drug users.
- Of Americans ages 12 years or older, 19.7 million battled a substance use disorder. Of those, approximately 74% of adults struggled with an alcohol use disorder, and 38% battled an illicit drug use disorder.
- One of every eight adults struggled with alcohol and drug use disorders simultaneously.

The cost of substance abuse (tobacco, alcohol, illicit drugs, prescription opioids) to society, including the costs related to health care, crime, and lost work productivity, exceeded \$820 billion (based on data from 2007–2013).⁷⁹

FDA has a website that lists consumers' frequently asked questions about home test kits for drugs of abuse: www.fda.gov/medical-devices/drugs-abuse-tests/drugs-abuse-home-use-test. This resource can be recommended to patients and, if applicable, their parents.⁸⁰

The symptoms of drug use are varied but may include withdrawal from normal activities, fatigue, red eyes, drowsiness, slurred speech, and chronic cough. The National Institute of Drug Abuse (www.nida.nih.gov) is a good resource for specific symptoms for the various drugs of abuse. Drug abuse tests may allow parents and caregivers to detect drug use early enough to affect the course of addiction.

Usage Considerations

Numerous products for detecting use of drugs are available in retail stores and pharmacies and through the internet. **Table 48–8** lists examples of tests and the substances that each test identifies.

TABLE 48–8 Selected Nonprescription Home Drug Abuse Tests				
TABLE 48–8 Selected Nonprescription Home Drug Abuse Tests				
Trade Name (Website)	Result Time to	Sample Collection	Testing Location	Detected Substances
At Home Drug Test (www.phamatech.com)	10 minutes	Urine	Home; send away for confirmation	Single-substance kits for cocaine and marijuana Multiple-substances kits

Trade Name (Website)	Time to Result	Sample Collection	Testing Location	Substances Detected
	Laboratory confirmation			12-panel kit: amphetamine, barbiturates, benzodiazepines, cocaine, marijuana, methadone, opiates, PCP, propoxyphene, valium 25-panel kit: amphetamine, barbiturates, benzodiazepines, cocaine, marijuana, methadone, opiates, PCP, propoxyphene, valium
				oxycodone, PCP
EZ Level Drug Test (www.ezlevel.com/collections/elttests) / (www.ezlevel.com/collections/drug-tests)	5 minutes 5 minutes	Urine. Testing device immersed in urine for 10 seconds. Strips absorb and test sections.	Home; qualitative results (Yes/No) for tested drugs based on color bands on test strip if negative or positive or detection limit of test.	Marijuana drug test; 5-panel drug test: amphetamine, barbiturates, benzodiazepines, cocaine, marijuana, opiates, PCP 12-panel drug test: amphetamine, barbiturates, benzodiazepines, cocaine, marijuana, opiates, PCP, propoxyphene
				propoxyphene
HomeTestNow (www.hometestnow.com)	5 minutes	Urine. Testing device immersed in urine for 30 seconds. Strips absorb and test control	Home; qualitative results (Yes/No) for tested drugs. Color bands appear on test strip if result is	12-panel instant urine dipstick test: amphetamine, barbiturates, benzodiazepines, cocaine, marijuana, methadone, opiates, PCP, propoxyphene

Key: MDA = 3,4-Methylenedioxyamphetamine; MDEA = 3,4-methylenedioxy-N-ethylamphetamine; MDMA = methylenedioxymethamphetamine; PCP = phencyclidine.

Home drug tests are marketed primarily to parents as an aid for determining drug use in their children. These tests are a means of obtaining results anonymously when drug use is suspected. Home drug testing, however, is not a substitute for open communication between parents and children regarding drug use.

Users of these tests may have questions about how soon and how long after its use can a drug be detected. Clearance rates for common drugs of abuse are given in [Table 48–9](#).⁸⁰ These data are only guidelines, and the times can vary significantly from these estimates based on how long the person has been taking the drug, the amount used, and the person’s metabolism.

TABLE 48–9 Examples of Estimated Times for Positive Drug Test		
Drug	How soon after taking drug will a positive drug test occur?	How long after taking drug will a drug test continue to be positive?
Amphetamine, methamphetamine	4–6 hours	2–3 days
Barbiturates	2–4 hours	1–3 weeks
Benzodiazepine	2–7 hours	1–4 days
Cocaine	2–6 hours	2–3 days
Ecstasy	2–7 hours	2–4 days
Marijuana	1–3 hours	1–7 days
Methadone	3–8 hours	1–3 days
Opiates	2–6 hours	1–3 days
Oxycodone	1–3 hours	1–2 days

Drug	How soon after taking drug will a positive drug test occur?	How long after taking drug will a drug test continue to be positive?
Phencyclidine	4–6 hours	7–14 days

Source: [Reference 81](#).

Samples of urine or hair are collected at home. The hair tests and some of the urine tests are mailed to a CLIA-certified laboratory, with results obtained by telephone or over the internet via a secure portal. For some of the urine tests, the user conducts a preliminary screening test in the home and then mails positive samples to a laboratory for confirmation. Other urine tests are performed only at home. Saliva tests are available, but they are currently marketed only to drug testing programs and employers.

Some of the test kits include telephone counseling (1) to help parents recognize the signs of drug use, (2) to assist in creating a family drug policy, and (3) to emphasize that parents should use the test to develop trust and open communication within their family members, rather than to intimidate them with the threat of random testing. Some telephone counseling programs provide referrals to rehabilitation and counseling services in the family's community.

Mechanism of Action

For the home urine tests, an immunochromatographic assay similar to the home pregnancy and ovulation tests is used for initial screening of a sample. Available testing devices include (1) a test cassette to which urine is applied and (2) a test device that is placed in the urine sample. In each test, a positive result for a particular drug is the absence of a line next to the drug name in the testing area. For a negative test, a line appears by the drug name and in the control area.

The laboratories use an enzyme-multiplied immunoassay technique to detect drugs in the urine samples. Gas chromatography–mass spectrometry is then used to identify the specific drug. Positive home urine samples sent to clinical laboratories for confirmation are checked for evidence of adulteration.

Substances such as water or household chemicals can be added to urine samples in an attempt to mask drug use.

Home urine tests detect drug use that occurred from several hours before testing to within 2–3 days of testing. The amount of drug found in the urine is affected by the time since consumption, the amount taken, and the amount of water consumed before sampling. Test results are reported as only positive or negative for a drug. Quantity or route of ingestion is not determined.

Hair testing detects trace amounts of ingested drugs that become trapped in the core of the hair shaft as it grows at an average rate of 1/2 inch per month. Drug use over a 90-day period can be determined from a hair sample of 1 1/2 inches.⁸¹ The presence of drugs is determined by radioimmunoassay techniques, followed by gas chromatography–mass spectrometry analysis to identify the specific substance. Hair tests report positive or negative results for a drug. For some tests, positive results are reported as a number that indicates low, medium, or high levels of use for all drugs except marijuana; the latter is reported only as positive or negative.

Usage Guidelines

See the box “Patient Education for Drug Abuse Tests.”

Interferences

Ingestion of decongestants, dextromethorphan, antidiarrheals, or cough medications containing codeine may cause false-positive results for home drug abuse tests. These items contain substances structurally related to certain drugs of abuse. Consumption of large quantities of poppy seeds or poppy seed paste may or may not cause a false-positive result for opiates, depending on the test’s sensitivity. Sensitivity standards for opiates have been raised to reduce the possibility of false-positive results.

Product Selection Guidelines

The criteria for selecting one drug abuse test over another include the drugs that are suspected of being used, the type of suspected use (i.e., casual vs. chronic), the length of time since last use, and the possibility that the suspected drug user tampered with the sample. The list of drugs that may be

identified varies with each kit. These tests can test for a single drug or up to 14 drugs.

In general, urine tests are better for detecting low-level, casual drug use. Hair testing detects longer-term use. It takes at least 5–7 days for hair to grow far enough from the scalp for testing purposes. Urine samples are subject to tampering by adding chemicals, diluting with water, or substituting someone else's urine sample. Some of the test kits include a temperature strip on the urine collection cup to ensure the sample is at body temperature. Parents may accompany their child to the bathroom to collect the urine sample. Hair samples, if taken directly from the person being tested, are not subject to tampering. Parents should weigh the possibility of tampering when deciding which type of test to choose.

Assessment of Drug Abuse Test Use

The length of time of suspected drug use and the types of drugs that are suspected will determine which type of drug abuse test to recommend. Whether the suspected user is likely to tamper with urine samples also should be considered. Finally, whether the suspected user takes legal prescription or nonprescription medications that may interfere with the test should be determined.

Patient Counseling for Drug Abuse Tests

When parents or caregivers ask for assistance in selecting a drug abuse test, health care providers should offer clinical advice and information about family counseling agencies. Counseling should emphasize the limitations of the tests for confirming drug use and, in the case of urine tests, for identifying anything more than the type of drug that is being abused. The box “Patient Education for Drug Abuse Tests” lists specific information to provide patients.

Patient Education for Drug Abuse Tests

Usage Guidelines for Urine Drug Abuse Tests

- Collect urine using the collection device included with the test. Do

not take urine from the toilet.

- Check the temperature of the urine sample immediately after collection using the temperature strip, if included. If the sample is not between 90°F (32°C) and 100°F (38°C), adulteration may have occurred.
- Immerse the test card in the urine sample for time specified in the instructions, usually 10–15 seconds, or until visible migration across the test panels has occurred. Place the device on a flat surface or leave it immersed in the sample. Do not allow urine to exceed the “max line.”
- Read the results when the “results ready” indicator changes to a pinkish red. Do not read the results 15 minutes or more after this indicator changes color or after the “results expired” indicator changes color.
- If no line appears in the control region, the test is invalid and should be repeated with a new card.

Usage Guidelines for Hair Drug Abuse Tests

- Follow manufacturer guidelines for proper hair sample collection for the specific test being use. For most tests, collect a hair sample, ½-inch wide and 1½ inches in length from the crown of the head, as close to the scalp as possible.
- Align the cut ends of the hair sample and place the sample in the collection package as directed. Do not collect hair from a hairbrush, comb, or clothing; there is no guarantee that the hair is actually from the person to be tested.
- Results are available approximately 3–9 days after receipt by the laboratory. To access results, call the manufacturer’s toll-free number and provide the code number accompanying the kit, or log into the secure portal to obtain the results.

Avoidance of Incorrect Results

- Drug tests on urine samples report only a positive or negative outcome. Neither the quantity of drug taken nor the method in which it was taken is determined.

- Drug tests on hair samples can report a low-, medium-, or high-level of drug use, but the use could have occurred as long as 90 days before testing.
- Cough medications that contain codeine or dextromethorphan, decongestants, antidiarrheals, narcotic analgesics, and possibly poppy seeds may cause false-positive test results.

When to Seek Medical Attention

- If the test is positive, seek the services of a drug rehabilitation organization, or contact a health care provider.

Evaluation of Patient Outcomes With Drug Abuse Tests

If a positive result is obtained with a drug abuse test in a minor, parents or caregivers need to consider potential problems with the test itself before concluding that drug use is confirmed. In addition, they must not assume that a negative result is accurate. Parents also should consider the testing window when evaluating results. For tests completed in adults, similar issues regarding how to address positive and negative results should be considered.

Blood Pressure Monitors

Hypertension, often an asymptomatic disease, affects tens of millions of Americans and provides an opportunity for home monitoring to improve outcomes. In 2017, the American College of Cardiology and the American Heart Association published new guidelines for hypertension management and defined the categories of blood pressure, as shown in [Table 48–10](#).^{82,83}

TABLE 48–10 ACC–AHA Categories for Blood Pressure

BP Category	Systolic BP (mm Hg)		Diastolic BP (mm Hg)
Normal	<120	AND	<80

BP Category	Systolic BP (mm Hg)		Diastolic BP (mm Hg)
Elevated	120–129	AND	<80
Stage 1 HTN	130–139	OR	80–89
Stage 2 HTN	≥140	OR	≥90

Key: ACC = American College of Cardiology; AHA = American Heart Association; BP = blood pressure; HTN = hypertension.

Source: [References 82](#) and [83](#).

When these guidelines were applied to the National Health and Nutrition Examination Survey (NHANES) data, the prevalence of hypertension among U.S. adults between 2013 and 2016 was shown to be 45%.⁸⁴ It has been demonstrated that pharmacists, using patient's home blood pressure results and telemonitoring, can individualize drug therapy regimens and help more patients reach their blood pressure goal.⁸⁵ A study that used traditional methods to compare the accuracy of home blood pressure devices with reference measures found differences between the two sets of blood pressure values. Specifically, the home devices were less accurate for systolic measures and in patients with a large arm circumference. Most of the values obtained with home blood pressure devices were not within 5 mm of readings obtained by the traditional method.⁸⁶

Many pregnant women are asked to monitor their blood pressure regularly to detect preeclampsia or other potential complications. Use of a home device provides both convenience and, if needed, multiple readings to guide interventions. An analysis of various automated home blood pressure devices found that very few have been validated officially for use in pregnancy. Nonetheless, one study found the reliability of data obtained with home blood pressure monitors was similar between validated and nonvalidated devices in this population.⁸⁷

Some of the advantages of home blood pressure monitoring are due primarily to the use of automated electronic devices. These devices are widely available and are cost effective. They also reduce user error and have been shown to

improve blood pressure control, improve medication adherence, and allow for more frequent measuring. Some disadvantages include lack of validation to ensure consistent accuracy and reliability, possible self-modification of drug therapy, and lack of medical supervision.⁸⁸ An assessment of hundreds of home blood pressure devices available worldwide found that <20% of those used on the upper arm, <9% of wrist cuff devices, and none of the >500 wearable devices had been validated (see the section “Digital Devices” for discussion of the validation process).⁸⁹ A number of resources are available to assist health care providers and to guide patients in determining which home blood pressure monitoring device is best for a given patient. Space prohibits the inclusion of details for each of these devices, and readers are encouraged to visit the referenced sites for the most recent information.

The reasons for inadequate control of blood pressure are multiple, but a significant factor is lack of patient motivation to take steps to control blood pressure, especially if the patient is asymptomatic, which leads to nonadherence with treatment strategies.

The consequences of untreated hypertension are well documented. Long-standing elevations in blood pressure can lead to damage to the heart, kidneys, lungs, eyes, and blood vessels, and to an increase in morbidity and mortality.

Treatment of high blood pressure often involves significant lifestyle changes (e.g., diet, exercise). Medications may cause adverse effects that impact adherence. Patient education and empowerment play a large role in improving patient adherence with efforts to control hypertension. Adherence, in turn, helps reduce morbidity and mortality, maintains or improves the patient’s quality of life, and improves the patient’s use of health care resources.

Teaching patients to take their own blood pressure at home is an excellent means of achieving blood pressure control. Home blood pressure monitoring gives patients a sense of control over their health and allows them to measure their progress toward a target blood pressure. Three general advantages of measuring blood pressure at home are the ability (1) to distinguish sustained hypertension from “white-coat hypertension” (i.e., measurements affected by being in the provider’s office); (2) to assess response to antihypertensive medication; and (3) to improve patient adherence to treatment.

Usage Considerations

The most popular choices for home blood pressure monitors are aneroid and digital. Monitors that measure pressure at the wrist and fingers have become popular, but the systolic and diastolic pressures vary substantially in different parts of the arterial tree. Finger monitors have so far been found to be inaccurate and are not recommended. Wrist monitors are typically smaller than the arm devices and can be used in obese people because wrist diameter is little affected by obesity.⁹⁰

Mechanism of Action

Blood pressure readings include two types of pressures: *systolic*, which indicates pressure at the time of contraction of the heart cavities, and *diastolic*, which indicates pressure at the time of dilation of the heart cavities. Blood pressure is measured indirectly by two methods: *auscultatory* (measurement of sound) and *oscillometric* (measurement of vibration). Aneroid meters involve auscultation with the use of a stethoscope to detect *Korotkoff's sounds*, which are produced by the motion of the arterial wall in response to changes in arterial pressure. *Oscillometric sensors*, which often are used with digital meters, measure blood pressure by detecting blood surges underneath the cuff as it is deflated. The detection device, which is usually indicated on the cuff with a tab or other marking, is placed directly over the brachial artery. The brachial artery can be found by palpating 1–2 inches above and just to the inside of the antecubital space. As cuff pressure increases during the measurement procedure, the brachial artery is compressed and blood flow is obstructed. As cuff pressure is gradually released, blood flow is reestablished and Korotkoff's sounds can be heard in different phases. Phase I, which corresponds to systolic pressure, can be identified when at least two consecutive "beats" are heard as cuff pressure is decreased. The nature of the sounds changes over the next three phases. Diastolic pressure is identified at the point the sounds disappear (phase V).

Interferences

Stress, tobacco smoking, and ingestion of caffeine-containing beverages can increase blood pressure. Some medications (e.g., pseudoephedrine) also may increase blood pressure.

Usage Guidelines

The actual measurement of blood pressure is a relatively simple procedure; however, many people consistently do it incorrectly. Blood pressure is naturally variable; therefore, proper technique is essential to reduce measurement variability and improve the quality of results. The normal range for blood pressure is established in patients seated in the resting state; any variation from this setting can produce inaccurate results.

Using the appropriate size cuff is essential to accurately measure a patient's blood pressure ([Table 48–11](#)). If the cuff is too small, blood pressure readings can be overestimated significantly by as much as 20–30 mm Hg. Several monitors are supplied with a large cuff; many others allow a large cuff to be purchased separately. For patients with arms too large for the largest size cuff, a wrist monitor may be a useful alternative. To obtain accurate readings with wrist cuffs, the patient must hold the wrist at heart level during the reading. Because these devices also are highly sensitive to changes in the wrist level, it is best to support the arm on a table with a pillow that will raise the wrist to the appropriate level. For the person who is doing the actual monitoring, following the steps outlined in the box “Patient Education for Self-Monitoring of Blood Pressure” will help improve the accuracy of blood pressure readings, regardless of whether they are taken in the health care provider's office, the pharmacy, or the home.

TABLE 48–11 Arm Circumferences to Determine Appropriate Blood Pressure Cuff Size

Arm Circumference (adult) ^a	Cuff Size
22–26 cm	Small adult cuff
27–34 cm	Regular adult cuff
35–44 cm	Large adult cuff
≥45 cm	Thigh cuff ^b

^a Determine arm circumference by measuring around the midpoint of the upper arm. Remeasure the patient's arm periodically, especially if he or she has recently gained or lost significant weight.

^b Consider a wrist monitor for patients whose arm circumference is >45 cm.

Source: [Reference 92](#).

Product Selection Guidelines

Of the two primary types of blood pressure–measuring devices, no single type is best for every patient. The choice of device is individualized according to characteristics such as the patient’s ability and willingness to learn, physical disabilities, patient preference, and the cost of the device. In general, aneroid devices are the least expensive. Depending on its features, a digital device can cost as much as a mercury column device. A discussion of the pros and cons of all three types of devices follows.

Aneroid Devices

Aneroid devices are the most accurate and reliable. They are lightweight, portable, and very affordable, and they pose no risk from mercury toxicity. They include several features that make patient instruction much easier. First, most devices come with a stethoscope attached to the cuff, which frees the patient from having to hold the bell of the stethoscope in place. Second, a D-ring on the cuff allows a single user to easily place the cuff on the arm. Third, a few manufacturers offer a gauge that is attached to the inflation bulb, making it easier to manipulate the equipment because there are fewer pieces to control. These monitors are considered the option of choice for home use, but they do require careful patient instruction and follow-up. Good eyesight and hearing are necessary for accurate readings with standard models. For patients with reduced visual capacity, however, devices with large-type print on the face of the gauge are available.

At the bottom of the face of each aneroid device is a small box. When the cuff is completely deflated and lying on the table, the needle of the gauge should rest in the box. If the needle is outside the box, the gauge needs recalibration. Many manufacturers sell recalibration tools to allow health care providers to adjust the devices.

Digital Devices

With advancing technology, digital devices have become more accurate, reliable, and easy to use; as a result, they have skyrocketed in popularity. These devices include *semiautomatic* (manually inflating), *fully automatic* (autoinflating), wrist, and finger blood pressure monitors. Features such as printouts, pulse monitor, digital clock, automated inflation and deflation, memory, large display, and D-ring for the cuff differentiate many of the devices. These features significantly affect the price.

A major drawback to digital monitors is the user's inability to determine whether the device is out of calibration. Patients should be advised to have their monitors checked at least annually by a health care provider for accuracy and to purchase a device that has been validated. The American Medical Association (AMA) assembled experts to establish criteria to determine which automated blood pressure devices used in clinics, communities, and the home setting are clinically accurate. These Validated Device Listing (VDL) criteria were fine-tuned with input from manufacturers, FDA, additional clinicians, and health care organizations. AMA maintains an updated list of validated devices on its website.⁹¹

If recommending a digital device, the provider should check the manufacturer's specifications to ensure that the monitor meets at least the accuracy standards set by the American National Standards Institute (ANSI). The ANSI standards for digital sphygmomanometers state that blood pressure readings between 20 and 250 mm Hg must not differ by >3 mm Hg or 2%, whichever is greater.⁹²

Assessment of Blood Pressure Self-Monitoring

Assessment should include determination of (1) why a patient wants to use a blood pressure monitor, (2) whether the patient has physical impairments that can interfere with proper use of the monitor, and (3) whether the patient can comprehend and follow instructions.

Patient Counseling for Blood Pressure Self-Monitoring

The health care provider should emphasize the importance of tracking blood

pressure values to monitor control of hypertension. Regular self-monitoring of blood pressure will illustrate positive effects of lifestyle changes and medication use in controlling the disorder. This reinforcement can improve patient adherence with prescribed therapies. The patient should be shown the proper technique for blood pressure monitoring and then be encouraged to return for a follow-up evaluation of his or her technique. Because of white coat hypertension, patients who measure blood pressure at home usually obtain lower results than those taken at the provider's office. The box "Patient Education for Self-Monitoring of Blood Pressure" lists specific information to provide patients.

Evaluation of Patient Outcomes for Self-Monitoring of Blood Pressure

Patients who measure blood pressure for diagnostic and monitoring purposes should be instructed on how to track values and how to discuss the values with their health care provider. Patients monitoring their blood pressure should be cautioned not to adjust their medications unless their provider instructs otherwise. Patients should be instructed to immediately contact their provider if they obtain elevated values and have any symptoms of high blood pressure, such as headache or blurred vision. Patient counseling and follow-up can improve outcomes in hypertensive patients by (1) motivating them to perform home monitoring of blood pressure; (2) guiding them in product selection; (3) training them to use devices appropriately; and (4) facilitating communication between the patient, the patient's family, and the patient's provider regarding any antihypertensive therapy.

Patient Education for Self-Monitoring of Blood Pressure

Precautions and Avoidance of Incorrect Results

- Keep a log of blood pressure readings and any circumstances that might have affected the reading (e.g., feeling nervous or being late for work).
- If home readings are being performed for diagnostic purposes, take readings at different times throughout the day and under different

circumstances.

- If readings are being done to determine adequacy of antihypertensive therapy, take the reading at the same time of day, preferably in the early morning soon after arising from bed.
- Allow plenty of time to relax before taking a blood pressure reading. Feelings of stress or pressure can elevate the blood pressure.
- Do not use tobacco products or drink caffeine-containing beverages for at least 30 minutes before taking a measurement. These activities can increase blood pressure.
- Wait 10–15 minutes after a bath and 30 minutes after eating to take a measurement. These activities can lower blood pressure.
- Some medications may increase blood pressure. Be alert for possible changes in blood pressure readings when starting or stopping medications.

Usage Guidelines

- Make sure the room is at a comfortable temperature.
- Sit in a comfortable chair, with your back supported and your feet facing straight ahead and placed flat on the floor.
- If using an arm cuff, place the arm to be measured on a table, making sure your upper arm is at heart level. Remove restrictive clothing from the arm.
- If using a wrist cuff, place pillows under the arm to be measured to bring the wrist up to heart level.
- Place the cuff on the arm to be measured. The cuff should be snug but not tight enough to restrict blood flow. Use the guidelines in Table 48–10 for selecting cuff size.
- Rest for at least 5 minutes in this position.
- Measure the blood pressure as directed in the product instructions. If using a stethoscope, listen for the Korotkoff's sounds as described here:
 - Phase 1: Sound begins as a soft tapping. Record the systolic pressure when two taps are heard in sequence.
 - Phase 2: Tapping sound becomes louder and is accompanied by a swishing sound or murmur.
 - Phase 3: Tapping sounds persist, but the swishing or

murmur sound stops.

- Phase 4: Tapping sounds are muffled or softened.
- Phase 5: Tapping sound stops. Record the diastolic pressure when the sound stops.

- Using the same arm, take two to three measurements separated by at least 2 minutes.
- Record the results, arm used, time and date of measurement, and name and time of last dose of any medications, including antihypertensive medications.
- Do not adjust blood pressure medications based on home measurements unless specifically instructed to do so by a health care provider.

When to Seek Medical Attention

- See a health care provider immediately for evaluation and treatment if readings are above limits set by your health care provider or above the limits stated in national guidelines, and if you are having symptoms such as headache or blurred vision.

Miscellaneous Home Tests and Technologies

As the market for home test products and wearable devices and shopping on the internet have exploded, new tests and technologies are becoming available with increasing frequency. Some newer technologies and devices provide patients with an opportunity to assess various parameters as part of a disease management program or from a preventive perspective. The growth of mobile phone apps and smartphone technologies for all current and future platforms enhances consumers' ability to self-diagnose and treat many health disorders.⁹³ Currently these mobile health apps are having positive and negative impacts on self-care. Concerns include development of apps with no expert involvement, lack of high-quality evidence to support and validate the app, incomplete features, and incorrect responses that lead to negative outcomes and patient harm.⁹⁴

A number of smart devices are available to monitor various parameters, such as blood pressure, blood oxygenation, and heart rate. Biobeat's wrist monitor provides an opportunity for continuous monitoring of these parameters along with cloud software and a mobile app for real-time data review by patients and their providers.⁹⁵

Devices such as the Apple Watch can be paired with a monitor such as the QardioArm Smart Blood Pressure Monitor to provide wireless data regarding systolic and diastolic blood pressure, heart rate, and detection of irregular heartbeat via the Qardio App. Some Apple Watches have the ability to monitor heart rate and generate an electrocardiogram. The Apple Heart Study, conducted by researchers at Stanford University School of Medicine, compared Apple Watch readings with electrocardiographic patch readings and found that the Apple Watch had a 71% positive predictive value for detecting cardiovascular irregularities that were confirmed to be atrial fibrillation.⁹⁶ SmartBP is a blood pressure management app from Evolve Medical Systems, LLC, that allows individuals to record, track, analyze, and share their blood pressure information using their iPhone/iPod touch/iPad devices and some Apple Watches.⁹⁷ A comparison of a wearable blood pressure device to industry standard devices for measuring blood pressure found an acceptable correlation between the two types of devices.⁹⁸

Many blood glucose monitoring devices are available without a prescription, yet a vast majority are obtained with a prescription because the device and necessary supplies are covered under prescription insurance. This process provides opportunities for health care providers to work with patients, review data stored on the device, and adjust therapies to achieve better outcomes. More recently, apps have been developed to add a more sophisticated layer of monitoring that includes incorporation of additional information such as medications, nutrition, exercise, and other health and lifestyle data points. However, many apps focused on self-management of diabetes have been shown to be lacking in timely and accurate education, adequate quality assurance processes, and appropriate advice for managing hypoglycemic and hyperglycemic results and for dealing with necessary alerts and warnings.⁹⁹ If patients are interested in using or are currently using one of these apps, they should discuss the advantages and disadvantages of this additional resource with their providers. Numerous websites evaluate these and many other health apps. Providers should help patients find the apps that best fit their needs and advise them to monitor their blood pressure regularly.

Technology and devices to assess sleep are another area of self-testing that is undergoing significant growth. The American Academy of Sleep Medicine (AASM) published clinical guidelines that provide recommendations for appropriate evaluation of obstructive sleep apnea and other sleep disorders. These guidelines specify that portable sleep-assessment monitoring devices record the following information: pressure-based airflow, pulse oximetry, heart rate, and respiration effort. AASM also suggests that other measures such as snore, body position to assess for estimation of positional apnea, and temperature-based airflow be included.¹⁰⁰

SleepView is a monitor that assesses airflow, respiratory effort, blood oxygenation, heart rate, snore, event detection, sleep time, and other assessments based on various body positions (supine, prone, left, right, and upright). Individuals interested in using the device need to work with their health care provider to obtain the SleepView kit. Data obtained with the device are uploaded to a secure portal so patients and providers both have access to and can discuss results and options for management of any issues identified.¹⁰¹ Other devices with similar technologies include Alice NightOne and the Watch PAT One.^{102,103} WatchPAT One collects sleep data and pairs with a patient's smartphone to transmit the data to a secure server. Through a series of algorithms, the data are analyzed and reported to the prescribing physician. The device is discarded once the testing is completed.¹⁰³

Test MyAllergy, an at-home allergy test kit that offers an opportunity to test for the presence of blood immunoglobulin E (IgE), is one way to assess whether symptoms are related to an allergen. Results, either positive or negative for the presence of elevated levels of IgE, are available within 30 minutes of obtaining a fingerstick blood sample. If the user wants more-specific information, the company also offers an Allergy 35 IgE antibody test. This test entails collection of a blood sample that is sent to the company's CLIA-certified laboratory for analysis, which usually is completed within 10 days. Per the manufacturer, this immunoassay determines the levels of antibody reactivity against specific allergens such as various grasses, ragweed, mold, foods, animal dander, dust mites, and many other substances. The process, which involves a test blotting procedure and a 2-spot blood card, is very similar to the ELISA tests offered by many laboratories. Medical experts are available to assist with data assessment and to develop an allergy management plan.¹⁰⁴

A home thyroid-stimulating hormone (TSH) test kit is available to provide

patients with data on their TSH level. The pituitary gland produces TSH, which in turn stimulates the thyroid to produce specific hormones. Hypo- and hyperthyroidism pose significant health risks, so identifying these disorders will lead to better treatments and outcomes. A fingerstick blood sample is applied to the provided collection card, which then is sent to a CLIA-certified laboratory. Results are typically available within 3 weeks via a secure online portal that can be accessed by the patient and any designated health care providers.¹⁰⁵

Selected miscellaneous home tests and wearable devices are described in [Table 48–12](#). Instructions for use are generally available from the manufacturer’s website or a site that sells the product. Following the general guidelines provided in this chapter also will help patients obtain accurate results.

TABLE 48–12 Selected Miscellaneous Nonprescription Home Tests			
Most of these products are sold by multiple manufacturers, retailers, and website marketplaces, and the vendors change regularly. Readers are encouraged to research each topic and identify options that best fit their practice or patient needs.			
Test (Website)	Purpose	Important Points	Additional Information
Alcohol screening tests (breath, saliva)	Prevents inappropriate alcohol consumption	Put nothing in mouth 15 minutes before or during the test. Follow timing directions carefully and use a timing device.	Semiquantitative BAC; saliva test strips can be used to detect alcohol in drinks.
Breast Self-Examination Aid	Makes breast self-examination easier and more comfortable	Examine breasts monthly. Self-examination does not take place of mammogram and professional examination.	Two-layer polyurethane breast shield or glove contains a small amount of silicone lubricant to reduce friction. Some kits come with instructional video (e.g., Aware, Sensa Touch).

Monistat Complete Care Vaginal Health Test ^a (www.monistat.com/vaginal-complete-care-products/vaginal-health-test)	Detects pH of vaginal secretions. (Color change based on vaginal acidity. Result is either normal or abnormal.)	pH ≥ 4.5 plus symptoms suggest yeast infection. pH ≥ 5 + symptoms suggest bacterial vaginosis or trichomoniasis.	Those with first-time yeast infection and those with pH ≥ 5 should see HCP for diagnosis. See chapter 8 for additional information.
TobacAlert (www.tobacalert.com , www.nymox.com) and Accutest NicAlert for saliva and urine (www.jantdx.com/product/accutest-nicalert-urine-screen/)	Detects tobacco use or exposure	Test detects cotinine, a metabolite of nicotine; test detects nicotine use or exposure in previous 48–72 hours. Dip strip in urine (TobacAlert, NicAlert) or saliva (NicAlert) sample, and read results in specified time.	Use of nicotine patch or gum can affect results. Secondhand smoke exposure may cause a positive result.
Test Me DNA Home DNA Paternity Testing Kit ^a (testmedna.com/home-dna-paternity-testing/); Home DNA Paternity Test (formerly IDENTIGENE DNA Paternity Test Collection Kit) (homedna.com/product/homedna-paternity;dnatesting.com/). Store-brand tests also are available.	Checks paternity of a child	Collect cheek cell samples from each participant: alleged father, child, and biological mother. Swabs are mailed to laboratory.	Kit is not available in all states. Results are available 2–5 days after sample is received by laboratory. Results are not valid for legal purposes (requires verified collection procedure and additional costs).
Reveal Home Menopause Test (urine) (www.americanscreeningcorp.com/drug-testing/reveal-menopause-test.asp); Thorne Menopause Test (saliva) (www.thorne.com/products/dp/menopause). Other saliva, urine, and blood test kits are	Urine test: detects FSH in urine Saliva test: measures various hormone levels	Urine positive test = FSH level >25 IU/L, which may indicate a woman is menopausal. FSH levels change during the menstrual cycle, so	Not a definitive diagnostic test for menopause. Diagnosis requires confirmation by HCP. Test kit is purchased, sample collected, sent to

available.	(cortisol, testosterone, estradiol, progesterone, DHEA)	the test should be done twice 1–2 weeks apart to confirm results.	laboratory for analysis and review by on-staff physicians.
Perimenopause test (www.everlywell.com)	Measures FSH, estradiol, and LH in blood sample	User purchases kit, registers kit on website, collects fingerstick blood sample, and sends sample to CLIA-certified laboratory.	Personalized results provided on portal and should be discussed with user's HCP to determine action steps.
Strep A tests ^b (Many brand-name and store-brand products are available.)	Detects strep throat infections	Same rapid test kit as that used in medical settings. Includes positive and negative control. Results provided in 5–10 minutes.	Positive test needs to be confirmed by HCP. Those with a negative test who are symptomatic also likely require follow-up with an HCP.
Home electrocardiogram monitors: Different manufacturers offer products (omronhealthcare.com/ekg/ ; www.theheartcheck.com ; www.alivecor.com/ ; www.pocketecg.com/pocketecg/).	Detects and records heart rhythm	Consumer and prescription versions. Device electrodes are placed on either one or both thumbs, or on the chest near the heart. Most devices come with an app for recording and storing data.	Device should be used in conjunction with HCP monitoring.

^a Store-brand product also are available.

^b Many brand-name and store-brand products are available.

Key: BAC = Blood alcohol concentration; FSH = follicle-stimulating hormone; LH = luteinizing hormone; DHEA = dehydroepiandrosterone; HCP = health care provider.

Key Points for Home Testing and Monitoring Devices

- To advise patients properly on selecting and using home testing or monitoring products, health care providers must be familiar with the procedures for each available product.
- Manufacturers continually introduce new products and modify current ones to provide more user-friendly versions. To keep up to date, providers should request product information from manufacturers by calling their toll-free numbers, visiting their websites, or contacting their sales representatives.
- FDA's website also should be checked frequently for problem reports, updates, and news on home tests.
- Patients who are using home tests or devices should be encouraged to follow instructions carefully and, if needed, to contact either their provider or the manufacturer's toll-free number for assistance.
- Health care providers should stress that the patient is self-testing, not self-diagnosing. Positive test results should be reported immediately to a provider for a definitive diagnosis and management of the disorder. Negative test results should be questioned when the patient is experiencing symptoms of a suspected disorder.
- If there is any question about the results, the patient should seek the advice of a health care provider.

Chapter 49: Adult Urinary Incontinence and Supplies

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Urinary incontinence (UI) is defined as the symptom of any involuntary leakage of urine.¹ Although most common in older adults, UI affects people of all ages, socioeconomic backgrounds, and ethnicities.² An estimated 25 million people in the United States are affected by UI,³ whereas more than 50 million may suffer from *overactive bladder* (OAB), whose primary symptom is a strong desire to void.⁴

UI is an underdiagnosed and underreported condition that has major psychosocial and economic effects. Feelings of embarrassment, denial, and misinformation prevent many people from seeking help, which may lead to anxiety, depression, and, possibly, social isolation.² Severe UI usually results in a loss of self-esteem and the ability to maintain an independent lifestyle. UI generally is recognized as a strong predictor of nursing home admission of older people.²

Direct costs associated with UI include the expenses for diagnosis, specific treatment, routine care, rehabilitation, and hospital and nursing home admissions. The direct costs of treating OAB with UI in adults older than 25 years were estimated at \$65.9 billion in 2007 with projected costs of \$82.6 billion in 2020.⁵

Despite the high prevalence of UI, fewer than half of community-dwelling adults with UI consult their health care provider.⁶ Many of these people accept the symptoms as a natural part of aging and use self-care strategies with little or no health professional guidance. Although they are reluctant to talk about UI, Americans spend \$2.3 billion annually on disposable incontinence products (e.g., pads, shields, guards, undergarments, briefs).⁷

Pathophysiology of Urinary Incontinence

Urination is a complex process, involving a coordinated effort by the bladder, urethra, and muscular components of the lower urinary tract, brain, and spinal

cord.⁸ Urine produced by the kidneys is propelled through the ureters to the bladder. The *detrusor muscle*, the smooth muscle layer of the bladder, gives tone to the bladder, relaxing as the bladder fills with urine and contracting during urination. The *bladder neck*, which joins the bladder and the urethra, is surrounded by smooth muscle, referred to as the internal sphincter, which either constricts to hold urine in the bladder or relaxes, permitting urine to flow through the urethra. *Micturition*, or voluntary control of urination, is maintained by contraction of the *external sphincter*, a striated muscle located at mid-urethral length. When relaxed, the urethra, which is surrounded by both smooth and striated muscle, allows urine to leave the body.

The bladder and the internal sphincter are innervated by the autonomic nervous system, and the external sphincter is innervated by the somatic or voluntary nervous system. Parasympathetic and sympathetic nerves innervate the smooth muscle of the bladder and urethra. Both α -adrenergic and β -adrenergic receptors are present in the urinary structures. The alpha receptors are located in the base of the bladder and the proximal urethra, and the beta receptors are found primarily in the body of the bladder detrusor. Stimulation of the alpha receptors causes contraction of the smooth muscles in the bladder neck and urethra, thus closing the bladder outlet. Stimulation of the beta receptors results in smooth muscle relaxation and allows the bladder to fill. As a result, sympathetic stimulation causes the bladder to retain urine. Parasympathetic cholinergic receptors are located throughout the bladder. Stimulation of these receptors causes the detrusor to contract, emptying the bladder. The *sacral center*, lying between vertebrae S2 and S4, acts as the relay center for information to and from the bladder, pelvic floor, and brain.

The capacity of the bladder is approximately 400–500 mL. When the bladder fills, stretch receptors in the detrusor wall transmit signals to the brain through the spinal cord, initiating the urge to urinate when the bladder is approximately half full. Under normal circumstances, adults can delay voiding for 30–60 minutes as a result of the short sacral reflex, which diminishes the urge to urinate by increasing contraction of the external sphincter and relaxing the detrusor muscle of the bladder. Bladder emptying usually is initiated voluntarily, causing relaxation of the external sphincter and contraction of the detrusor. Normal urination results in complete emptying of the bladder, with little or no residual urine (≤ 50 mL). Any disruption in the integration of musculoskeletal and neurologic function can lead to loss of control of normal bladder function and UI.⁹

Clinical Presentation of Urinary Incontinence

UI is a symptom that can be caused by external factors and by anatomic, physiologic, and pathologic factors that affect the urinary tract.^{2,10–12} In many cases, multiple and interacting factors contribute to UI. The risk of UI is strongly associated with aging. Additional risk factors for UI, some at least partially reversible, have been identified ([Table 49–1](#)).^{2,10–12} Identification of the cause(s) of UI is essential for its assessment and successful management.

TABLE 49–1 Risk Factors for Urinary Incontinence

Medical Disorders or Procedures
Benign prostatic hyperplasia (BPH)/transurethral resection of the prostate (TURP)/prostatectomy
Childhood nocturnal enuresis
Diabetes
Fecal impaction
Immobility/chronic degenerative disease
Impaired cognition, acute or chronic
Metabolic disorders (hyperglycemia, hypercalcemia)
Neurologic disorders (spinal cord injury, neuropathy)
Obesity (moderate–morbid)
Pregnancy/vaginal delivery/episiotomy
Stroke
Physiologic Factors
Estrogen depletion
High fluid intake (leading to polyuria and bladder capacity overload)
Low fluid intake (leading to concentrated urine and bladder irritation that worsen symptoms)
Pelvic floor muscle weakness

Lifestyle Factors
High-impact physical activities (e.g., running, jumping jacks)
Smoking
Other Factors
Caucasian race
Environmental barriers
Medications (Table 49–2)

Source: Adapted from [references 2](#) and [10–12](#).

Age-related changes in the bladder and urinary tract may contribute to an older person's vulnerability to UI. With age, the kidney's ability to concentrate urine diminishes, resulting in larger urine volumes. In addition, age-related hypotrophic changes in bladder tissue lead to frequent urination and nocturia, whereas decreased muscle tone of the bladder, as well as the bladder sphincters and pelvic muscles, contributes to the potential for reduced urine control. This loss of control, combined with diminished mobility and reaction time, predisposes older people to UI.¹³

In women, the loss of estrogen causes a decrease in bladder outlet and urethral resistance, as well as a decline in pelvic musculature, all of which increase the likelihood of UI. In addition, estrogen loss results in atrophic changes in the vaginal and urethral mucosa, disrupting the vaginal flora and leading to atrophic vaginitis and chronic urethritis. These conditions, in turn, may cause urinary frequency and urgency, dysuria, urinary tract infections, and UI. Compared with the male urethra, the female urethra is shorter and exerts less resistance to intravesicular pressure. Consequently, obesity, chronic cough, and jarring exercise, which all increase intra-abdominal pressure, result in an extra load on the bladder. As such, these factors can overwhelm the relatively low resistance offered by the short female urethra. Childbirth, gynecologic procedures, and muscle atrophy from aging also weaken the female pelvic floor muscles, thereby decreasing support for the bladder.

Without adequate support, positioning of the bladder becomes distorted (known as *cystocele* or *anterior wall prolapse*) and can result in urethral kinking, with subsequent poor bladder emptying. These conditions may result in chronic obstruction of the bladder, again leading to UI from urine volume overload.

Men often develop prostatic enlargement beginning in their middle to late 40s, which results in urethral obstruction, leading to decreased urinary flow rates, increased residual volumes, detrusor instability, and possibly overflow incontinence. Paradoxically, prostatectomy to relieve bothersome symptoms related to benign prostatic hyperplasia (BPH) can result in stress urinary incontinence (SUI) caused by incidental injury to the internal sphincter.

UI can be described broadly as transient or chronic. *Transient UI* usually is of sudden onset and secondary to acute illness (e.g., urinary tract infections) or to any disease that causes acute confusion (e.g., respiratory disease, myocardial infarction, septicemia) or immobility (e.g., fracture, injury), preventing the person from reaching a toilet independently or in time. Many other conditions and medications can cause or contribute to transient UI ([Table 49–2](#)).^{2,9} Managing these conditions may resolve UI in some patients but only reduce the severity of symptoms in others. Chronic UI often is related to neurologic or other chronic conditions, such as intrinsic sphincter deficiency, BPH, or cystocele.¹⁴ UI can be classified as overactive bladder (OAB), SUI, mixed incontinence (OAB plus SUI), overflow incontinence, or functional incontinence, depending on the underlying etiologies.

TABLE 49–2 Reversible Conditions That Cause or Contribute to Urinary Incontinence

Conditions Affecting the Lower Urinary Tract
Urinary tract infections, atrophic vaginitis/urethritis, fecal impaction, pelvic floor prolapse, hyperglycemia, hypercalcemia
Drug Adverse effects
Polyuria, frequency, urgency: caffeine, diuretics, alcohol, acetylcholinesterase inhibitors
Urinary retention: anticholinergics, antidepressants, hypnotics/sedatives, antipsychotics, narcotics, muscle relaxants, antihypertensives (calcium channel blockers), β -adrenergic agonists, α -adrenergic agonists
Urethral relaxation: α -adrenergic blockers

Urethral pressure imbalance (SUI): cough from ACE inhibitors
Increased Urine Production
Metabolic disorders (e.g., hyperglycemia, hypercalcemia), excessive fluid intake, volume overload, venous insufficiency with edema leading to nocturia
Inability or Unwillingness to Reach a Toilet
Dementia, delirium, illness/injury that interferes with mobility, psychological conditions

Key: ACE = Angiotensin-converting enzyme; SUI = stress urinary incontinence.

Source: [References 2](#) and [9](#).

Recognition of signs and symptoms of UI is an essential first step in providing treatment advice. Patients often delay discussion or do not seek medical evaluation of UI with their health care providers. Therefore, it is important for providers to inquire about potential UI symptoms when clinical evidence or patient inquiries indicate existence of such conditions. Open-ended questions such as “What problems are you having, if any, with your bladder?” and “How often do you experience urine leakage?” can be used to begin this dialogue. An awareness of signs such as the odor of urine or appearance of wetness also is necessary to identify potential patients suffering from UI. [Table 49–3](#) lists observed and reported signs and symptoms commonly associated with particular types of UI. Encouraging the use of a 24-hour voiding diary, paper or electronic, is a helpful tool in diagnosing and managing UI.^{15,16} In a voiding diary, patients can document fluid intake, amount of urine voided, episodes of urine leakage, urge to urinate, and activity at the time of leakage or sense of urgency.

TABLE 49–3 Common Signs and Symptoms of Urinary Incontinence (UI) by Type

Type of UI	Urgency	Frequency	Volume of Loss	Nocturia	Other
Urge	Frequent	>8 times per day	Large amount of urine loss: >100 mL and	>1 time per night	Inability to reach toilet following urge

Type of UI	Urgency	Frequency	Volume of Loss	Nocturia	Other
			may empty completely		to void
Stress	Occasional	Urine leakage during physical activity, lifting, coughing, sneezing; if severe, urine loss on ambulating	Small-moderate urine loss, depending on level of activity	Rare	Ability to reach toilet in time to complete void
Overflow	Hesitancy	Straining to void	Decreased or incomplete urine stream; dribbling	Frequent	Sensation of bladder or abdominal fullness, and incomplete bladder emptying

OAB occurs in both men and women, and its incidence increases with age. This condition is characterized by sudden and profound urinary urgency, usually accompanied by frequency (urinating more than 8 times daily) and nocturia (two or more awakenings at night to pass urine). The condition often, but not always, is accompanied by *urge incontinence* (UI; involuntary urine leakage with urgency).^{2,9,13} OAB usually, but not always, is attributable to uninhibited contractions of the detrusor muscle, referred to as *detrusor instability*. Other terms describing detrusor instability are *detrusor hyperreflexia*, *detrusor hyperactivity with impaired bladder contractility*, and *bladder instability*.

Neurogenic causes of detrusor instability include dementia, stroke, Parkinsonism, suprasacral spinal cord injury, multiple sclerosis, and medullary lesions. Detrusor instability of neurologic origin is referred to as *hyperreflexia*. Nonneurogenic causes of detrusor instability include bladder irritation caused by infection or interstitial cystitis (*bladder pain syndrome*), obstruction (e.g., BPH, cystocele), bladder stones, and tumors. Excessive beverage intake and some therapeutic agents (e.g., diuretics, alcohol) can exacerbate symptoms of UI as a result of increased filling of the bladder. Bethanechol also can lead to UI through cholinergically mediated contraction of bladder smooth muscle.

SUI is characterized by involuntary leakage of urine with sudden increases in abdominal pressure associated with sneezing, laughing, coughing, exercising, and lifting. SUI is the most frequently encountered type of UI in women, except in the very old (>75 years), in whom OAB is most common. Symptoms of SUI may occur in some men after transurethral resection of the prostate and radical prostatectomy.¹³ Symptoms in women are exacerbated by pregnancy and obesity, which also increase intra-abdominal pressure. This involuntary leakage is believed to be caused by hypermobility of the bladder neck or weakness of the urethral sphincter and pelvic floor muscles. *Hypermobility* refers to displacement of the bladder neck and urethra during physical exertion; it occurs when the supporting pelvic muscles have been weakened as a result of vaginal childbirth and aging. The weakening of the urethral sphincter can be secondary to vaginal or urologic surgery, trauma, aging, or inadequate estrogen, or it may be neurologic in etiology.¹⁷ Drug-related causes of SUI include α -adrenergic antagonists such as prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin, which cause urethral relaxation ([Table 49–2](#)).

Overflow incontinence, an involuntary urine loss associated with overdistention of the bladder, is observed in 7%–11% of incontinent older patients.² Symptoms include dribbling, reduced force and caliber of urinary stream, urgency, and a sensation of incomplete voiding. The two main causes are outlet obstruction and/or an underactive bladder (detrusor) muscle. Outlet obstruction can be caused by BPH, urogenital tumors, pelvic organ prolapse, or previous anti-incontinence surgery. Dysfunctional bladder contractility can result from diabetic or alcoholic neuropathy, lower spinal cord injury, radical pelvic surgery, or medications that have anticholinergic properties, such as antihistamines, antipsychotics, narcotics, tricyclic antidepressants, muscle relaxants, and medications used to treat UI. These medications can cause overflow incontinence by blocking cholinergically mediated bladder contractions, thereby inhibiting normal bladder function.

Mixed incontinence, most common in women, consists of the combination of OAB and SUI.² Although the term *mixed UI* generally is applied to women, men with outlet obstruction resulting from BPH may exhibit mixed symptoms of OAB and overflow incontinence. Men also may exhibit mixed symptoms as a result of SUI attributable to radical prostatectomy or transurethral resection of the prostate combined with OAB.

Functional incontinence is described as urine loss caused by factors such as

physical or cognitive impairment, which interfere with a person's ability to reach toilet facilities in time or to perform toileting tasks.² Causes of this type of UI are many and include stroke, diminished mobility, impaired cognitive function or perception, environmental barriers, use of sedative and hypotensive agents, poorly controlled severe pain, and psychological unwillingness to release urine in the proper place. Because many functionally impaired people may have other types of UI, functional incontinence should be a diagnosis of exclusion.

The consequences of UI are considerable. Many people are embarrassed by such a condition and refrain from discussing their urinary problems with their primary care providers. Some people with UI believe it is a normal consequence of aging, rather than a symptom of underlying disease or anatomic change. Social isolation occurs because the incontinent patient avoids social interaction to prevent the embarrassment and rejection that often accompany UI. In turn, social isolation leads to depression. Intimate contact and sexual activity with the patient's partner also can decrease. Attempts to limit episodes of involuntary urine loss by restricting fluid intake can cause dehydration and hypotension, whereas skin irritation and ulceration caused by long exposure to urine result in "diaper rash" and possibly pressure injuries.²

The caregivers of incontinent older patients are under stress because of the tedious and time-consuming care needed to deal with the problems of UI at home. Often, the loss of urine control leads to a drastic reduction in quality of life, and in some cases, placement in a long-term care facility.^{2,18} Falls and fractures may be potential risks associated with repeated trips to the bathroom caused by UI or urgency symptoms in the absence of incontinence.¹⁹

Treatment of Adult Urinary Incontinence

Treatment Goals

The goals of treatment of UI are to cure incontinence or to reduce the severity of symptoms, avoid complications, and improve the patient's quality of life. When incontinence aids are used as part of self-management in UI treatment, additional goals are to control or treat skin breakdown (diaper rash), control

the odor of leaked urine, and contain urine in the undergarment.

General Treatment Approach

Treatment is individualized for the type of UI. The four major categories of intervention are behavioral modification, use of devices, pharmacologic treatment, and surgical treatment. [Figure 49–1](#) outlines the self-management of adult UI.

Nonpharmacologic Therapy

Behavioral techniques decrease the frequency of UI in most patients, have no reported adverse effects, and do not limit future therapies.² These techniques generally require patient and caregiver involvement and continued practice to be most successful. Three types of behavioral techniques, listed in order of increasing need for patient involvement, are toileting assistance, bladder training, and pelvic floor muscle training. Behavioral techniques now are the accepted first-line therapy in treating all forms of UI, except overflow incontinence.²⁰ A behavioral modification program involving pelvic floor muscle training and behavioral techniques was found to prevent the development of UI in continent older women.²¹ Providers should educate patients about the role of behavioral therapy in the prevention and management of UI.

Toileting assistance includes routine or scheduled voiding performed at fixed, regular intervals (every 2–4 hours); habit training, or scheduling voiding to match patterns in those who have natural voiding patterns; and prompted voiding. In prompted voiding, patients are trained to void only if the need is voiced on direct questioning. They are checked for wetness and praised for maintaining continence and trying to void.

Bladder training consists of education, scheduled voiding with systematic delay, and positive reinforcement. Patients are taught to delay voiding when the urge occurs and to use tactics to increase urine volume and the interval between voids. Bladder training is recommended for urge or mixed incontinence but often is difficult to achieve in cognitively impaired or frail older people.

Training of pelvic floor muscles aims to improve urethral closure pressure by

activating the striated muscles of the urethra and the underlying pelvic floor muscles. Two components of training have been established. Early improvement (reduction of urine leakage within 1 week of beginning pelvic floor muscle exercises) may be achieved by some women who learn “the knack maneuver,” or volitional precontraction. The *knack maneuver* describes learning to contract pelvic floor muscles in anticipation of and during increases in intra-abdominal pressure (e.g., coughing). This maneuver alone has demonstrated the capacity to reduce SUI.²² In addition, pelvic floor muscle training, also known as Kegel exercises or pelvic floor exercises, is designed to strengthen the voluntary periurethral and perivaginal muscles, giving the patient more control of micturition, thereby reducing UI.² Kegel exercises, which have been used successfully for SUI and OAB, are performed by squeezing the pelvic muscles as if to stop the flow of urine. The contractions should be held for about 10 seconds and then released for 10 seconds; 3–4 sets of 10 contractions per day are generally recommended.^{2,23} It is important to advise patients that the response to pelvic muscle exercises is delayed.

The exercises may be augmented by the use of vaginal weights or biofeedback techniques. Biofeedback can facilitate learning pelvic muscle exercises. Direct electrical stimulation of the pelvic floor muscles with vaginal or anal probes or surface electrodes has been used with limited success in SUI, urge UI, and mixed UI. FDA has recently approved several nonprescription devices that utilize electrical stimulation and/or biofeedback. ApexM, designed for home use, treats SUI, urge UI, and mixed UI in women. After 90 days of proper use, women experienced a 90 percent reduction in bladder leakage. On average, SUI symptoms are resolved within 12–14 weeks, whereas complete resolution of symptoms of urgency/OAB may take longer.²⁴ Attain, similar in design to ApexM, includes visual biofeedback and a guided exercise program.²⁵ Innovo, another FDA-cleared, nonprescription device for SUI, is a noninvasive device similar in appearance to exercise shorts.²⁶ The device delivers 180 pelvic floor contractions in 30 minutes; when used 5 times per week, this device resolved dryness in 87% of users after 12 weeks.²⁷

Radiofrequency energy treatment (Lyrette, formerly Renessa), a nonsurgical approach to SUI, is available in a urologist’s office.²⁸ The treatment, which uses low temperature to cause natural collagen to become firmer, produced improvements in 3 of 4 women and nearly 60% eliminated the use of pads.²⁹ Another option available only through a provider’s office is the NeoControl pelvic floor therapy system.³⁰ This is a pulsating magnetic chair that uses

directed magnetic fields to induce pelvic muscle contractions. Patients generally require 20- to 30-minute treatments twice a week for 8 weeks or longer. FDA approved this device for treatment of SUI incontinence, OAB, and mixed UI. Application of mechanical pressure to support the urethra is evident in the age-old advice to women with SUI to cross their legs before coughing or sneezing to prevent urine leakage.³¹ Similarly, various devices have been used by prescription for UI, including elevating devices to support the bladder neck (pessary, tampon, prosthesis); urethral occlusive devices (urethral plug or insert, caps, expandable urethral devices, urethral shields); external collection systems (condom catheters, female urinals); penile compression devices; and catheterization (intermittent, indwelling, suprapubic).² Poise Impressa Bladder Supports³² and Revive Reusable Bladder Supports³³ are nonprescription internal products cleared by FDA for the temporary management of SUI. The core of Impressa bladder support is made from flexible, medical-grade silicone, surrounded by a soft, nonabsorbent polypropylene covering with a polyester and rayon string to help make insertion and removal easy. Revive is a reusable silicone ring that comes with 31 strings; after 31 uses, the device should be discarded. Similar to a tampon, each bladder support comes in a smooth plastic applicator and is inserted into the vagina to gently lift and give support to the urethra. Designed to reduce or stop urine leakage in women with SUI, Impressa is available in three sizes to adapt to a woman's unique internal shape; Revive is available in one size. A recent review of mechanical devices found inconsistent results, insufficient evidence to compare one device with another, and no evidence to compare mechanical devices with other forms of treatment.³⁴

Although uncommon in the treatment of OAB, surgery can successfully treat SUI and overflow incontinence. Surgery is an option when nonpharmacologic and pharmacologic therapies have failed or the patient wants definitive treatment. The aims of continence surgery are to elevate the bladder neck, support the urethra, and increase urethral resistance.^{2,35} Some surgical options include urethral bulking agents (collagen), sling operation, tension-free vaginal tape, artificial sphincter insertion, needle bladder-neck suspension, retropubic suspension, urinary diversion, and bladder denervation. It should be noted that surgical treatment for SUI can instigate or exacerbate symptoms of urgency.

Pharmacologic Therapy

The type of UI influences the choice of treatments, making a prior medical

evaluation essential. Inappropriate use of systemic nonprescription products and incorrect use of absorbent undergarments and pads before a proper evaluation may result in unnecessary expense, inappropriate treatment, and possibly unnecessary changes in the patient's lifestyle and psychological well-being. For that reason, an overview of the pharmacologic measures for specific types of UI is presented here. Most medications used to treat these disorders are prescription products; however, a nonprescription form of oxybutynin, Oxytrol for Women, was approved in 2013. OAB or UI may be treated with anticholinergic medications, which facilitate urine storage by decreasing uninhibited detrusor contractions. Oxybutynin (Oxytrol for Women) provides a nonprescription option for women ages 18 years and older with urinary symptoms consistent with OAB (e.g., two of the following three symptoms for at least 3 months: frequency, urgency, and incontinence). The transdermal patch is applied every 4 days to a clean, dry, and smooth area of the skin on the abdomen, hips, or buttocks. Application sites need to be rotated with each patch. Common adverse effects include skin irritation at the patch application site, constipation, and dry mouth. Sleepiness, dizziness, and blurry vision also may occur. Thus, driving or operating machinery is not advised until patients know how they will react to the patch. If symptoms do not improve, women should seek a medical referral.³⁶

Prescription anticholinergic medications such as darifenacin, oxybutynin chloride, solifenacin, tolterodine, fesoterodine, and trospium are used frequently for OAB and urge UI. Mirabegron, a beta-3 adrenergic agonist approved for the treatment of both conditions, is an alternative to anticholinergic medications. For patients who do not respond or who cannot take anticholinergic medication, onabotulinumtoxinA offers significant relief from symptoms of OAB and urge UI.³⁷

Other prescription medications that have less evidence of clinical efficacy and raise concerns about risks of adverse effects include propantheline, imipramine, hyoscyamine, and nifedipine. Flavoxate, FDA approved for urinary tract symptoms, is not effective according to the results of four placebo-controlled trials.³⁵ Diphenhydramine (see [Chapter 11](#)) and dicyclomine are used occasionally for UI. Providers should counsel patients about the potential adverse effects that occur more frequently with diphenhydramine than with the prescription products. Sedation, dry mouth (a problem for denture users and patients with gastroesophageal reflux disease, dysphagia, or stroke), dizziness, constipation, and confusion can be significant problems in older

patients. Contraindications to the use of diphenhydramine and other anticholinergic medications include many conditions (e.g., narrow-angle glaucoma, peptic ulcer, urinary tract obstruction, gastroesophageal reflux disease, uncontrolled hyperthyroidism) that occur more often in older patients. Because of these concerns, diphenhydramine and other anticholinergic medications are considered potentially inappropriate medications in older patients and are included in the most recent release of the Beers list.³⁸

SUI often is treated with agents that increase outflow resistance through alpha-receptor stimulation that enhances contraction of the bladder-neck muscles.² A commonly recommended nonprescription drug is pseudoephedrine (see [Chapter 11](#)).^{2,17} The dose of pseudoephedrine is 15–30 mg 3 times daily, starting with the lowest dose, especially in older people. Use of nonprescription medications for UI is an off-label indication and must be approved by a primary care provider. Caution should be used, however, when initiating such therapy in patients with hypertension and/or cardiac arrhythmias. Providers should advise patients to monitor their blood pressure and pulse, and to report any new occurrences of heart palpitations or fainting. Common adverse effects of pseudoephedrine include insomnia, headache, tachycardia, elevated blood pressure, dizziness, nervousness, agitation, and tremor.

Topical vaginal estrogen therapy is most useful in SUI with underlying vaginitis and urethritis caused by estrogen deficiency; several randomized controlled trials of vaginal estrogen have shown a decrease in urgency and incontinence.^{39,40} Therapy with estrogen vaginal cream usually is initiated with daily application and tapered to several times weekly applications; benefits are usually seen in 4–6 weeks. Other vaginal estrogen options include the vaginal ring and vaginal tablets. In women, only topical estrogen should be advised because placebo-controlled studies have shown that oral estrogen therapy is not effective and that systemic therapy is associated with potentially serious adverse effects, including venous thromboembolism, heart attack, stroke, and breast cancer. Estrogen can be used in combination with α -adrenergic agonists; however, the combination is only slightly more effective and can be associated with more adverse effects and increased therapy cost. The antidepressant imipramine, which also acts as an adrenergic agonist, has been suggested when α -adrenergic agonists and estrogens have failed. Duloxetine, a selective serotonin and norepinephrine reuptake inhibitor currently approved for the treatment of depression, post-herpetic neuropathy, and

diabetic neuropathy, is moderately effective in managing SUI.⁴¹ The treatment of overflow incontinence is directed by the underlying cause. In BPH, prescription α -adrenergic antagonists (terazosin, doxazosin, tamsulosin, alfuzosin, silodosin, prazosin) or 5-alpha-reductase inhibitors (finasteride, dutasteride) can be used to reduce the degree of outlet obstruction. Compared with 5-alpha-reductase inhibitors, α -adrenergic antagonists have a much faster onset of effect (several days). Because of a relatively high rate of orthostatic hypotension, prazosin is not recommended for therapy of UI. Prescription agents, such as bethanechol chloride, may be initiated if the bladder has insufficient contractile strength, such as after receiving general anesthesia. Its efficacy is not well established in long-standing hypotonic bladder, however, and it is associated with potentially serious adverse effects. In neurogenic bladder, bethanechol appears to be most effective when starting therapy as soon as possible after the occurrence of neurologic-induced incontinence. Surgery for BPH often is necessary. Catheterization, usually intermittent, is combined with frequent attempts to void as a last resort when medical and surgical corrections have failed.

Treatment of functional and iatrogenic incontinence requires evaluating the patient's entire medical status, medication history, and environment. UI resulting from medications can be resolved by initiating alternative treatments. Underlying dysfunctions, such as pain related to rheumatoid arthritis and decreased mobility, can be remedied by medical and environmental changes that make using the toilet possible or easier within the limitations of the patient's functional status. Often an assessment by physical or occupational therapists can be useful in enhancing physical function.

Use of Urinary Incontinence Supplies

Absorbent undergarments and pads are used to protect clothing, bedding, and furniture while allowing the patient to have independence and mobility. Although absorbent products are beneficial, they should be used only after a thorough and complete physical examination. Medicare, Medicaid, and other private insurers typically cover catheters and related supplies, but Medicare does not cover absorbent undergarments or pads, except during hospital and skilled long-term care visits. Medicaid will cover such bladder control supplies, but coverage varies by state. Prematurely initiating the use of absorbent protective products relieves the discomfort and obscures the cause of UI. Because correction of the cause may be possible, the premature acceptance of

UI may have significant financial, social, and psychological consequences.

Product Selection Guidelines

The type of absorbent product selected depends on several factors²:

- Type and severity of UI
- Functional status
- Gender
- Availability of caregivers
- Patient preference
- Cost
- Convenience

Health care providers need to discuss these factors with patients and their caregivers when helping them select absorbent garments and pads, which are available as reusable or disposable products ([Table 49–4](#)). This discussion is particularly important for low-income patients who often do not have the economic flexibility to purchase absorbent products; they may be forced to resort to ineffective substitutes such as toilet paper or tissue products. Many people attempt to extend the life of disposable products by layering flushable tissue over the pad. The tissue also is easier to dispose of in public places. However, its reduced wicking capacity can expose the skin to more moisture, creating the potential for breakdown. Some patients may be inclined to use low-cost menstrual pads that may be effective in some cases; however, these products contain materials that are specific to absorbing blood, not urine. Given the wide variety of available products, a resource guide published by the National Association for Continence (NAFC) may be invaluable in helping patients select a product.⁴²

TABLE 49–4 Selected Adult Incontinence Product Features^a

Trade Name	Absorbency	Size	Characteristics
Undergarments			
Assurance Slip-On Protective Undergarment ^b	Moderate-heavy leakage	One size	One-piece design; no buttons or tapes
Attends Undergarments Super Absorbency	Moderate leakage		Reusable elastic belts

Trade Name	Absorbency	Size	Characteristics
Depend Undergarments Easy Fit Elastic Leg/Adjustable Straps Regular & Extra Absorbency	Moderate leakage	One size; fits hip sizes up to 65 in.	Soft, cloth-like outer cover; reusable hook and loop strap tabs
Depend Undergarments Elastic Leg/Button Straps Regular & Extra Absorbency	Moderate leakage	One size; fits hip sizes up to 65 in.	Soft, cloth-like outer cover; reusable button strap tabs
Depend Undergarments Elastic Leg Extra Absorbency	Moderate leakage	One size	Soft, cloth-like outer cover; reusable button strap tabs
Depend Underwear Extra & Super Plus Absorbency	Heavy leakage	S/M, L	Feels and wears like underwear
Depend Refastenable Underwear Extra & Super Plus Absorbency	Heavy leakage	S/M, L/ XL	Feels and wears like underwear; 4 refastenable tabs
Prevail Underwear	Heavy leakage	S, M, L	For men and women; look and feel like underwear; pull-on
Briefs			
Attends Briefs	Heavy leakage	Y, S, M, L	Refastenable tapes
Attends Briefs with Waistband	Heavy leakage	M, L	Waistband
Depend Fitted Briefs Regular & Overnight Absorbency	Heavy leakage; overnight absorbency absorbs 30% more urine than regular absorbency	M, L	Six refastenable tapes plus elastic leg and waist; wetness indicator
TENA Briefs	Heavy leakage	Y, S, M, L	Refastenable tabs
Pads			
Attends Pads	Light leakage; medium-, extra-, super absorbency	8.5, 10.5, 12.5 14.5, 18 in. long	

Trade Name	Absorbency	Size	Characteristics
Poise Liners	Very light absorbency	6.5 in. long	
Poise Extra Coverage Liners	Very light absorbency	7.5 in. long	
Poise Thin Pads Light Absorbency	Light leakage	8.5 in. long	Elasticized sides
Poise Pads Regular Absorbency	Light leakage	8.5 in. long	Elasticized sides
Poise Pads Extra Absorbency	Light leakage	9.5 in. long	Elasticized sides; one end wider
Poise Pads Extra Plus Absorbency	Light-moderate leakage	11 in. long	Elasticized sides; one end wider
Poise Pads with Side Shields Ultra Absorbency	Light-moderate leakage	11 in. long	
Poise Pads with Side Shields Ultra Plus Absorbency	Moderate leakage	13 in. long	Pad-like comfort with guard-like absorbency; one end wider
Serenity/TENA Dry Active Liners	Light leakage	Regular and long	
Serenity/TENA Active Ultra Thin Pads	Light-moderate leakage	Regular and long	
Serenity/TENA Stylish Ultra Thin Pads with Wings	Light leakage	One size	Form fitting, sleek, and super absorbent
Serenity/TENA Anywhere Ultra Thin Pads	Heavy leakage	Long	
Serenity/TENA Anywhere Ultra Thin Pads	Moderate leakage	Regular	
Serenity/TENA Pads Moderate	Moderate leakage	Regular and long	
Serenity/TENA Pads Heavy	Heavy leakage	Regular and long	

Trade Name	Absorbency	Size	Characteristics
Serenity/TENA Ultimate Pads	Heavy leakage	One size	
Serenity/TENA Overnight Pads	Heavy leakage; overnight use	One size	Longest pad
Serenity/TENA InstaDRY Heavy Pads	Heavy leakage	One size	Fast-absorbing pad
Guards			
Attends Guards Super Absorbency	Light-moderate leakage	One size	Curved fit
Conveen Drip Collector	Dribbling or light leakage; adheres to underwear; designed for men	3- and 4-oz capacity	
Depend Guards for Men	Light-moderate leakage	One size	Anatomic design with elasticized pouch and cup-like fit
Serenity/TENA Guards Super Absorbency	Moderate-heavy leakage	One size	
Serenity Guards Super Plus Absorbency	Heavy leakage	One size	

^a Products change often; for current product availability, refer to these websites: www.depend.com, www.poise.com, www.serenity.com.

^b Manufacturer markets other products similar to the Depend line but offers a lower price point.

Key: Y = Youth; S = small; M = medium; L = large.

In 2012, NAFC recommended the following eight national quality performance standards for disposable adult absorbent products⁴³:

1. *Rewet rate*: a measure of a product's ability to withstand incontinent

episodes between changes

2. *Rate of acquisition*: a measure of the speed at which urine is drawn away from the skin
3. *Retention capacity*: a measure of a product's capacity to hold fluid
4. Sizing options: availability of sizes ranging from youth and small adult to extra-large and double-extra-large adult
5. Safety: absence of components, including additives, that are listed in any federal regulatory agency as being considered "unsafe"
6. Presence of a *closure system*: mechanism that allows the product to be opened and refastened
7. *Breathable zones*: an acceptable minimum air flow in side "wings" of the product sufficient to release trapped body heat and gaseous body perspiration in the pelvic region
8. *Performance of elastics*: provision of evidence of fit and functionality of containment of body waste, without sacrificing comfort

The disposable product market has been a multimillion-dollar industry since the 1990s. These products work in the same manner as children's disposable diapers. They are designed to absorb urine; provide a moisture barrier to protect clothes, bedding, and furniture; and minimize skin contact with urine. For maximum absorbency, products containing an absorptive gel of superabsorbent polymers may be preferable. Urine is jelled in the matrix of the absorbent layer, minimizing its contact with skin. Reusable incontinence undergarments may offer a more affordable option. These products resemble underpants with a waterproof crotch and are designed to hold a reusable panty liner. The newest option is reusable incontinence undergarments that resemble standard underwear but have the absorbency of disposable briefs. These undergarments have a unique crotch design made of several layers of wicking fabric that quickly pulls moisture away from the skin. They are available for men and women in a variety of leakage control levels. Reusable incontinence underwear is constructed of waterproof outer fabrics ranging from lace to nylon floral prints, making them an attractive and affordable option for patients with an active lifestyle. A comparative evaluation of the performance and cost-effectiveness of four key absorbent product designs demonstrated significant and substantial differences between products and considerable individual variability in preference. Cost-effective management with absorbent products may best be achieved by allowing users to choose combinations of designs for different circumstances.⁴⁴

The capacity of each disposable product corresponds to the needs of the patient:

- Guards/shields: 2–12 oz. (60–360 mL), light–heavy capacity
- Undergarments: 12–18 oz. (360–540 mL), moderate–heavy capacity
- Briefs: 28–36 oz. (840–1100 mL), moderate–heavy capacity

Patients with small amounts of leakage (e.g., dribbling), as occurs in SUI or overflow incontinence and after urologic surgical procedures, may require only a pad or a shield.^{45,46} A recent systematic review of absorbent products suggests that disposable insert pads are best for leak-through prevention; they also are the most acceptable and preferred design for women with light UI.⁴⁷ In a similar study, guards were preferred for light UI in men.⁴⁸ If larger amounts of urine are lost with UI, as often occurs with detrusor instability, products with a larger capacity would be more appropriate. Many products designed for overnight (heavy) use tend to have the largest capacities.⁴² Booster or doubler pads or inserts also are available to prevent leaks and increase the absorbency of current absorbent products.

Another important issue is the functional capacity of the patient. If the patient needs assistance with absorbent garments, the caregiver may find that briefs or diapers with “roll-on” bed application and adhesive closures are useful. Securing the product may be an important issue. Close-fitting underwear is recommended. Some garments or shields have adhesive strips or belts to hold them in place. The use of belts may require assistance from a caregiver. Of course, comfort and leg security from urine leakage are important. Many product lines offer elastic legs or contoured shapes. Caregivers and patients should consider products designed for the differences between male and female anatomy when selecting large-capacity products.^{45,46}

Protective underpads often are used in conjunction with briefs and undergarments for extended duration activities, such as sleeping and sitting. Both bed and chair pads are available, and the provider should inquire about the need for additional protection. The underpad should have a known capacity, a waterproof duration of several hours, and an ability to remain intact when wet. Bed pads are available in sizes from 16 by 24 in. to 30 by 36 in. For chairs, a 16- by 18-in. pad should be used.⁴⁶

Complications From Absorbent Products

Because the use of absorbent products increases the risk of skin irritation and maceration, these products should be checked every 2 hours. With continual urine loss, it is recommended that the absorbent material be changed every 2–4 hours. The use of skin protectants (barrier creams, ointments), as in diaper rash, is appropriate. If a rash occurs, the same treatment as that described for infants is indicated (see [Chapter 36](#)).

Urine odor is an embarrassing problem. Nonprescription products containing chlorophyll (e.g., Derifil, Pals, Nullo) or vitamin C can be recommended to help decrease urine odor. However, frequent checks for wetness and prompt changes of soiled pads and garments are preferable to efforts to mask the odor.

The healing of skin wounds may be delayed in the patient with skin wetted by urine. Any skin breakdown needs to be reported to the primary care provider. This serious complication should not be treated with nonprescription products without medical supervision.

UI products that are not available from the pharmacy or specialty supply store may be obtained by contacting the National Association for Continence (NAFC), PO Box 1019, Charleston, SC 29402-1019; 1-843-377-0900, 1-800-BLADDER; fax: 1-843-377-0905; or www.nafc.org.

Complementary Therapies

Nutritional deficiencies of protein, calcium, vitamin C, zinc, magnesium, and vitamin B₁₂ have been proposed as possibly contributing to the development of UI.⁴⁹ Of these, the relationship between vitamin B₁₂ deficiency and UI has been established.⁵⁰ A B₁₂ deficiency may lead to diminished neurosensory input regarding bladder fullness or to inappropriate neurologic stimulation of the bladder, causing detrusor instability. Many factors, such as spicy and acidic foods (e.g., caffeine, alcohol, citrus fruits), tobacco, dyes (e.g., Federal Food, Drug, and Cosmetic Yellow No. 5), food preservatives, and sugar substitutes (i.e., aspartame), may cause urinary frequency and urgency with the potential for UI. Cranberry may be effective in preventing UTI recurrence in generally healthy women,⁵¹ but it can worsen overactive bladder symptoms. The acidity of cranberry can irritate the bladder, and its diuretic action may increase

urinary frequency.

Several herbal products have been suggested to support patients with UI, including phytoestrogens (e.g., soybean, flaxseed), saw palmetto and pygeum (African plum), St. John's wort, and bearberry (uva-ursi) teas. Good clinical evidence from recent rigorous studies showed that saw palmetto is not effective in improving lower urinary tract symptoms related to BPH.^{52,53} In addition, there is no evidence from controlled studies that other aforementioned herbal products significantly improve lower urinary tract symptoms.⁵⁴ Patients should be advised to consult with their PCPs before using any of these products for UI. An in-depth discussion of saw palmetto and pygeum is presented in [Chapter 51](#).

Algorithm: Adult Urinary Incontinence

FIGURE 49–1 Self-care for adult urinary incontinence. Key: OAB = Overactive bladder; PCP = primary care provider; SUI = stress urinary incontinence; UI = urinary incontinence.

Assessment of Adult Urinary Incontinence and Supplies: A Case-Based Approach

Because of the public's general lack of sufficient medical knowledge about the different types of UI, some patients (or their caregivers) may attempt self-diagnosis and treatment without consulting their primary care providers. Self-diagnosis could lead to inappropriate treatment. Therefore, it is imperative that providers inquire about a proper medical evaluation before recommending nonprescription products, including absorbent products. Use of nonprescription medications for off-label indications must be recommended by a primary care provider.

Armed with the patient's history and proper diagnosis, the provider can answer questions appropriately and aid in the selection and proper use of devices and medications that treat this disorder.

Cases 49–1 and 49–2 illustrate the assessment of adult patients with UI.

Case 49–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Information Gathering	
1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient complains of episodes of a “weak bladder,” and “I have the urge to go more than 8 times in a day, and sometimes I don't make it to the bathroom in time.” The first incident occurred 3 months ago. As a result, she has restricted her fluids and limited her activities. She has not seen her primary care provider.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	“The ‘leakage’ occurs unexpectedly at no particular time. It is really causing issues at work.”
c. Description of the patient's efforts to relieve the symptoms	“I have been using extra absorbent feminine pads. I usually can get to the bathroom in time, but when leakage does happen, the urine soaks the pads.”
d. Patient's identity	Jamie Scott
e. Patient's age, gender, height, and weight	43 years old, female, 5 ft 2 in., 146 lb
f. Patient's occupation	High school gym teacher
g. Patient's dietary habits	Vegetarian diet, 3 cups of coffee/tea per day, 1 glass of wine daily
h. Patient's sleep habits	Usually get 7–8 hours of uninterrupted sleep.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Occasional use of acetaminophen for headaches multivitamin daily.

Relevant Evaluation Criteria	Scenario/Model Outcome
j. Allergies	NKA
k. History of other adverse reactions to medications	None
l. Other (describe) _____	Lives with partner
Assessment and Triage	
2. Differentiate patient's signs/symptoms and correctly identify the patient's primary problem(s).	Characteristics of Ms. Scott's urine leakage are consistent with overactive bladder with urge incontinence.
3. Identify exclusions for self-treatment.	None. However, Ms. Scott should be encouraged to seek a diagnosis for her UI before relying on incontinence products.
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Recommend a trial of Oxytrol for Women 3.9 mg/day patch. If symptoms do not improve within 2 weeks, patient should seek medical referral. (2) Refer Ms. Scott to her primary care provider or gynecologist for evaluation of urge incontinence. (3) Recommend a pad or shield for light urine leakage. Reusable incontinence underwear also may be an option for her active lifestyle. (4) Suggest avoidance of frequent use of caffeine.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	See Figure 49-1 .

Relevant Evaluation Criteria	Scenario/Model Outcome
	Ms. Scott should be offered a trial of Oxytrol for Women 3.9 mg/day patch. She should be advised to consider using pads, shields, or reusable incontinence underwear, as needed, for light urine leakage. These products would offer more protection than feminine pads. She should be counseled on the benefits of alcohol reduction.
6. Describe the recommended therapeutic approach to the patient or caregiver.	“Oxytrol for Women is recommended for the self-care of symptoms of overactive bladder, specifically the sudden and urgent need to urinate. If symptoms persist, a medical referral will be necessary.”
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	“Oxytrol for Women has been shown to be a safe and effective treatment for overactive bladder. Medical evaluation may be necessary for persistent symptoms to determine the type of incontinence and the need for a prescription medication or device.”
Patient Education	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver:	“Oxytrol for Women is recommended for the self-care of symptoms of overactive bladder, specifically the sudden and urgent need to urinate.”
a. Appropriate dose and frequency of administration	“Apply one 3.9 mg/day Oxytrol for Women patch to the skin every 4 days. It is a thin clear patch.”
b. Maximum number of days the therapy should be employed	“Apply the patch no more than 2 days per week. Select 2 days of the week (e.g., Sunday and Wednesday) and maintain a consistent schedule.”
c. Product administration procedures	“Remove the patch every 4 days and apply a new patch to a different area. The patch may be applied to the abdomen, hip, or buttock. Contact with water during bathing, swimming, showering, or exercising will not change the way Oxytrol works.
	If an Oxytrol patch falls off, try sticking it back into place. If it does not stick well, put on a new patch and leave it on only for the rest of your wearing time. Do not change your patch removal schedule.

Relevant Evaluation Criteria	Scenario/Model Outcome
	Do not wear more than one Oxytrol patch at a time. Using extra skin patches will not make the medicine more effective. Never cut a skin patch.
	Use baby oil or mild soap and water to remove any adhesive residue that stays on your skin. Avoid using harsh soaps, alcohol, nail polish remover, or other solvents that could irritate your skin.
	After removing a patch, fold it in half so that it sticks together. and throw it away in a place where children or pets cannot get to it."
d. Expected time to onset of relief	"Symptoms may improve within 3-4 weeks but could be seen as early as 2 weeks. Results are generally seen by 12 weeks."
e. Degree of relief that can be reasonably expected	"Usage may result in reduction of symptoms by as much as 75%."
f. Most common adverse effects	"The Oxytrol for Women patch may cause skin irritation where the patch was applied, dry mouth, and constipation.
	The Oxytrol patch may burn your skin if you wear the patch during an MRI procedure. Remove the patch before undergoing the MRI.
	Incontinence pads: may cause skin irritation, rash, maceration, and breakdown."
g. Adverse effects that warrant medical intervention should they occur	"If skin irritation near patch is severe, discontinue product use."
h. Patient options in the event that condition worsens or persists	"If symptoms persist, see your primary care provider or urologist for further follow-up. If urine loss is continual, change absorbent undergarments every 2-4 hours."
i. product storage requirements	n/a
j. specific nondrug measures	See the box "Patient Education for Adult Urinary Incontinence and Supplies" for behavioral measures to reduce and improve incontinence symptoms.

Relevant Evaluation Criteria	Scenario/Model Outcome
Solicit follow-up questions from patient or caregiver.	(1) “What if the symptoms don’t improve?”
	(2) “What if the incontinence product does not provide enough protection?”
Answer patient’s or caregiver’s questions.	(1) “If symptoms do not improve, see your primary care provider.”
	(2) “You may select a product with higher absorbency according to the amount of urine leakage.” (See Table 49–4.)
Evaluation of Patient Outcome	
9. Assess patient outcome.	“If symptoms do not improve within 2 weeks of using Oxytrol, consult with your primary care provider for further treatment and evaluation.”

Key: MRI = Magnetic resonance imaging; n/a = not applicable; NKA = no known allergies; UI = urinary incontinence.

Case 49–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Information Gathering	
1. Gather essential information about the patient’s symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient wants to use cranberry capsules for a recent problem of “inability to empty my bladder.” He heard about a product for urinary heath during a recent radio broadcast. He has been quite healthy,

Relevant Evaluation Criteria	Scenario/Model Outcome
	and this new problem is affecting his social life.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	He often wakes up 2-3 times per night to urinate.
c. Description of the patient's efforts to relieve the symptoms	Frequent trips to the bathroom
d. Patient's identity	Joe Thomas
e. Patient's age, gender, height, and weight	56 years old, male, 5 ft 10 in., 220 lb
f. Patient's occupation	School bus driver
g. Patient's dietary habits	Beer, 2-3 drinks on weekends
h. Patient's sleep habits	Frequent nighttime awakenings to urinate
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Hypertension: currently takes lisinopril 10 mg daily.
	Diabetes type II: metformin 500 mg BID
j. Allergies	NKA
k. History of other adverse reactions to medications	None
l. Other (describe) _____	n/a
Assessment and Triage	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Mr. Thomas's urine leakage may be consistent with overflow incontinence. He is currently taking no medications for urinary symptoms; he should see his PCP or urologist for reevaluation of the therapy prior to starting any dietary supplement or other nonprescription treatment.
3. Identify exclusions for self-treatment.	Mr. Thomas is a male who has not been evaluated by a PCP or a urologist.

Relevant Evaluation Criteria	Scenario/Model Outcome
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer Mr. Thomas for further evaluation of overflow incontinence. (2) Recommend nondrug measures and products to control his symptoms. (3) Recommend nondrug measures and products until he can see his PCP. (4) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Mr. Thomas should consult a PCP or other health care provider for further evaluation prior to using any nonprescription medication, prescription medication, or incontinence product.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Once current therapy has been evaluated and other causes eliminated, alternative prescription drug therapy may be suggested for reducing the symptoms of overflow incontinence. An absorbent guard may be appropriate for persistent symptoms."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"Medical evaluation is necessary to assess the cause of your symptoms prior to starting any drug therapy."
Patient Education	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver:	See the box "Patient Education for Adult Urinary Incontinence and Supplies."
a. Appropriate dose and frequency of administration	See the box "Patient Education for Adult Urinary Incontinence and Supplies."

Relevant Evaluation Criteria	Scenario/Model Outcome
b. Maximum number of days the therapy should be employed	See the box “Patient Education for Adult Urinary Incontinence and Supplies.”
c. Product administration procedures	See the box “Patient Education for Adult Urinary Incontinence and Supplies.”
d. Expected time to onset of relief	n/a
e. Degree of relief that can be reasonably expected	See the box “Patient Education for Adult Urinary Incontinence and Supplies.”
f. Most common adverse effects	“You may experience irritation, rash, maceration, and breakdown of the affected skin.”
g. Adverse effects that warrant medical intervention should they occur	“You should check for skin irritation every 2 hours.” See the box “Patient Education for Adult Urinary Incontinence and Supplies.”
h. Patient options in the event that condition worsens or persists	“If urine loss is continual, change absorbent undergarments every 2–4 hours. See your primary care provider or urologist for further follow-up.”
i. Product storage requirements	n/a
j. Specific nondrug measures	See the box “Patient Education for Adult Urinary Incontinence and Supplies.”
Solicit follow-up questions from patient or caregiver.	“What if the incontinence product does not provide enough protection?”
Answer patient’s or caregiver’s questions.	“You may select a different product with higher absorbency based on the amount of urine leakage.” (See Table 49–4.)
Evaluation of Patient Outcome	
9. Assess patient outcome.	Contact the patient in a couple of days to ensure that he made an appointment and sought medical care

Key: n/a = Not applicable; NKA = no known allergies; PCP = primary care provider.

Patient Counseling for Adult Urinary Incontinence and Supplies

The health care provider's role in self-treatment of UI includes educating patients about the condition; recommending medical evaluation, as appropriate, that is based on an initial evaluation of signs and symptoms; assisting patients and caregivers in selecting products to reduce the risk of urine leaking to outer garments; and avoiding factors that can aggravate the condition. Patients should be provided with information to help them understand UI. The box "Patient Education for Adult Urinary Incontinence and Supplies" lists specific information to provide patients regarding the use of incontinence supplies. An excellent resource for patient education is the Simon Foundation for Continence, PO Box 815, Wilmette, IL 60091; 1-800-23Simon; or www.simonfoundation.org.

Patient Education For Adult Urinary Incontinence and Supplies

The objectives of self-treatment are (1) to reduce or eliminate symptoms of urinary incontinence (UI), (2) to control or treat skin irritation caused by contact with urine, (3) to control the odor of urine leaked from the bladder, (4) to control leakage of urine to outer garments, and (5) to prevent other complications such as falls and social isolation. For most patients, carefully following product instructions and the self-care measures listed here will help to ensure optimal therapeutic outcomes.

- Consult a primary care provider or urologist for a thorough examination before resorting to permanent use of absorbent undergarments or shields. Many cases of UI are reversible with treatment.
- Absorbent products are designed to absorb urine; to provide a moisture barrier to protect clothes, bedding, and furniture; and to minimize skin contact with urine.
- Base selection of absorbent products on the amount of leaked

urine:

- Guards/shields: 2–12 ounces (60–360 mL), light–heavy capacity
- Undergarments: 12–18 ounces (360–540 mL), moderate–heavy capacity
- Briefs: 28–36 ounces (840–1000 mL), moderate–heavy capacity

- Choose briefs or diapers with roll-on bed application and adhesive closures (for patients who are unable to change themselves).
- If additional protection is needed during sleeping and sitting, select absorbent bed or chair pads to use with absorbent undergarments.
- Check skin for irritation or maceration every 2 hours, even when absorbent garments are used.
- If urine loss is continual, change absorbent undergarments every 2–4 hours, and consult your primary care provider or urologist if UI symptoms worsen.
- If desired, use skin protectants labeled for diaper rash to protect the skin (see [Chapter 36](#)).
- If desired, use products containing chlorophyll, such as Derifil, Pals, and Nullo, to help decrease odor. However, continue frequent skin checks and frequent changes of absorbent undergarments.
- If pressure injuries (open sores) occur in an immobile patient, the caregiver should not attempt to treat the ulcers with nonprescription products and should instead consult a primary care provider.
- Identify and eliminate foods, liquids, or other substances that can irritate the bladder (e.g., coffee, tea, soda, alcohol, chocolate, acidic juices, tomato-based sauces, spicy food, artificial sweeteners, nicotine).
- Avoid excessive intake of liquid. Drink enough to produce about a cup of urine every 3–4 waking hours on average. Do not drink large amounts of liquid after 5 PM.
- Avoid products that irritate the urethra and bladder. Use cotton underwear, avoid scented powders or bath products, and use white toilet paper.
- Follow instructions for behavioral therapy and medications for

incontinence if prescribed by your primary care provider or urologist.

Evaluation of Patient Outcomes for Adult Urinary Incontinence and Supplies

At follow-up, the provider should find out whether the pharmacologic therapy is effective, whether the recommended incontinence product is comfortable and easy to use, and whether leakage from the undergarment or odor is a problem. If leakage is occurring, the absorbency and/or type of product should be reassessed. Patients who have problems with odor may need to use deodorizers. The patient or caregiver also should be asked whether the skin, especially in the perivaginal and perianal areas, is being checked for breakdown. Redness or skin irritation call for the use of skin protectants. Questioning about occurrence of urinary tract or vaginal infections also is appropriate. Such infections may indicate a need to change undergarments more often or to use another type of incontinence product. These measures will prevent prolonged skin contact with urine. In addition, the provider should monitor the effectiveness of other prescription medications and behavioral therapies for UI. The patient should be asked about adverse effects associated with the specific medication he or she may be prescribed.

Providers also should evaluate whether the use of incontinence products and other treatments has allowed patients to resume their normal lifestyles and social interactions. If these objectives are not being met after an adequate duration of any pharmacotherapy, the medication dose and type should be reviewed. Alternative absorbent products also should be considered. The patient should be encouraged to seek further advice from his or her primary care provider on treatment options.

Key Points for Adult Urinary Incontinence and Supplies

- UI is a common treatable condition that is often cured or improved with therapy.
- Because the cause of UI may be multifactorial, the patient should receive a comprehensive medical evaluation before a therapy plan is developed.
- A variety of treatment options, including drug therapy, behavioral therapies, devices, incontinence aids, and surgery, are available.
- Currently only one nonprescription pharmacologic option, Oxytrol for Women, a 3.9 mg daily patch, is available for overactive bladder and UI.
- Incontinence aids are designed to absorb urine; to provide a moisture barrier to protect clothes, bedding, and furniture; and to minimize skin contact with urine.
- The selection of absorbent products is based on the amount of urine leakage.
- Providers can play an important role in educating patients about UI; performing assessment and triage and referring for medical evaluation, if needed; counseling on the selection and appropriate use of prescription and nonprescription incontinence products and the avoidance of aggravating factors; and monitoring patient response.

Chapter 50: Introduction to Dietary Supplements

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The Food and Drug Administration (FDA) defines *dietary supplements* (DS) as vitamins, minerals, herbs or other botanicals, and amino acids; dietary substances used to supplement the diet by increasing dietary intake or concentrates, metabolites, constituents, and extracts; or any combination of these stated ingredients.¹ Many terms have been used to describe DS, including *nutraceuticals*, *natural products*, *supplements*, *herbs*, *botanicals*, and *phytochemicals*. DS most often are grouped into the natural products category of complementary and alternative medicine (CAM) or integrative health (IH), according to the National Institutes of Health (NIH).² The term *complementary* refers to the use of natural products in addition to conventional medicine; *alternative* is the use of natural products in place of conventional medicine; *integrative* combines both natural and conventional approaches in a coordinated and purposeful way.² For the purposes of this chapter, herbs, vitamins, and similar products will be referred to as DS. FDA also uses this designation, because it relates to the intended use, namely for oral use only and for supplementing the diet. Indeed, consumers use DS not only to supplement the diet but also to maintain health and wellness. Some consumers also use DS to treat symptoms of medical conditions, despite FDA legislation that prohibits DS manufacturers from marketing products for this purpose unless the specific DS have undergone extensive review and been preapproved by FDA for a specified health claim.

Use of Dietary Supplements

Prevalence and Indications for Use

The National Health Interview Survey (NHIS), which is administered every 5 years to approximately 34,000–40,000 U.S. citizens, includes questions on complementary health approaches. The 2012 survey listed the use of non-vitamin and non-mineral natural products as 17.7% in adults older than 18 years and 4.9% in children ages 4–17 years.^{3,4} As shown in [Table 50–1](#), therapeutic use

of vitamin and mineral products in adults with multiple chronic conditions is more prevalent than use of the top 10 CAM approaches.⁵ In children ages 2–8 years, about 40% are given DS containing vitamins or minerals, despite their generally having adequate nutrient intake.⁶ All statistical data for DS use collected by the 2017 NHIS have yet to be published; partial results were released in November 2018. A significant increase in the use of yoga and meditation practices in children and an increased use of yoga, meditation practices, and chiropractors in adults have been preliminarily reported.⁷

TABLE 50–1 Top 10 Complementary and Alternative Medicine Practices Used by Adults With Multiple Chronic Conditions

Therapy Type	Total Study Population (n = 33,557)	Percent Use
Multivitamin or multimineral	17,493	52.7%
Vitamin	11,662	34.8%
Mineral	9891	28.4%
Non-vitamin or herbal therapy	5974	17.9%
Mind-body therapy	4127	12.5%
Chiropractic or osteopathic	2993	9.1%
Massage	2951	8.8%
Movement therapy	2162	6.6%
Special diets	1027	3.0%
Homeopathy	718	2.2%

Source: [Reference 5](#).

The National Health and Nutrition Examination Survey assessed adults' motivations for using DS.⁸ The primary reasons cited were to improve overall health (45%), maintain health (33%), and promote bone health (25%). Among adults ages 60 years and older, DS were used for site-specific conditions involving the bones, heart, and joints, whereas younger adults, ages 20–39

years, used DS to provide energy and immunity. Women frequently used calcium for bone health, whereas men used DS for heart health and lowering of cholesterol levels. The use of DS in the form of vitamin and mineral supplements also has been reported to contribute substantially to meeting the dietary reference intakes (DRIs) of key nutrients. Despite this use, some key nutrients such as vitamins C, D, and K and magnesium remain below the estimated average requirement for almost half of the U.S. population.⁹

The 2012 NHIS cited the following indications for CAM use in children (listed in order of prevalence): back or neck pain, other musculoskeletal disorders, head or chest cold, anxiety or stress, attention-deficit/hyperactivity disorder, and insomnia.⁴ When DS were considered as a separate CAM modality, indications for their use in children were less specific and involved diverse health conditions.⁴

Commonly Used Dietary Supplements

By 2024, the DS market is projected to generate approximately 57 billion US dollars, an increase of 18 billion dollars since 2019. Annual increases in market size have been steady, rising approximately 2–4.5 billion US dollars each year since 2016.¹⁰

Reported sales data for top DS differ according to the purchase location and may differ from actual consumer-use data. The most commonly used non-vitamin, non-mineral supplements in adults include fish oil, glucosamine, and chondroitin or a combination of these DS; pre- or probiotics; melatonin; and coenzyme Q10.³ In children, the most commonly used non-vitamin, non-mineral products are fish oil, melatonin, pre- and probiotics, echinacea, and garlic.⁴ Popular single-ingredient vitamins and minerals include vitamin D, calcium, and vitamin C.

Among all DS, vitamins and minerals remain the top-selling supplements, primarily because they are used across all life stages. Many Americans do not consume sufficient nutrient-dense foods, such as fruits and vegetables, resulting in inadequate intake of several vitamins and minerals relative to the Institute of Medicine's estimated average requirements or adequate intake levels.⁹ Even with DS use, some adults do not meet the estimated average intake of some nutrients.⁹ Knowing which DS are commonly used by adults and children will benefit pharmacists who are likely to be asked to assist with

product selection, provide directions for proper use, and counsel on safety considerations.

Attitudes and Predictors of Use

Many studies have measured predictors of CAM use and, more specifically, use of natural products such as DS.^{3,7} For most U.S. adults, common predictors for DS use include being female; being 45–64 years of age; having a college or higher degree; being of White, Asian, Pacific Islander, American Indian, or Alaskan Native descent; living in the western United States (i.e., West North Central, Mountain, and Pacific states); and having a current self-rated health status of very good to excellent.^{3,7} Having a higher socioeconomic status, defined as “not poor” or “near poor,” and having private health insurance also are predictors of high DS use.⁷ Users of DS also are more likely to be physically active and are less likely to smoke.⁷

Among children, use of non-vitamin, non-mineral natural products was twice as likely to be reported if the parent also used a CAM modality (9% vs. 4%).⁴ When vitamins and minerals were included, predictors of their use in children included being from a family with a higher level of parental education and family income, being from a family with private health insurance, living in the western United States, and being non-Hispanic white.⁴ DS use was more common in children who have a higher disease burden, a greater number of health conditions, and a greater number of primary care provider visits in the preceding 12 months.⁴

Older adults, ages 61–69 years, are frequent DS users and are more likely to have chronic conditions and to use concomitant prescription medications.¹¹ As such, this population is at an increased risk for drug–drug and drug–disease state interactions with DS. Individuals who cited general wellness as their rationale for use were 16 times more likely to consume DS. Other factors that appear to be highly predictive of DS use include having an attitude that the DS will work and having a history of receiving health care from CAM providers, such as acupuncturists, chiropractors, faith healers, herbalists, or homeopaths.¹¹ The findings suggest that the most important predictor of DS use is preservation of health, regardless of an individual’s assessment of his or her own health status, medical history, or use of concomitant medications.¹¹

Television was the most commonly reported source of DS information (73%),

followed by magazines and radio (both 30%), newspapers (13%), friends (8%), and store displays (5%).¹¹ Data on DS advertising spending, by media, support the highest prevalence of spending on magazine (46.6%) and television (43.7%) advertisements.¹² Segmentation of advertising by gender, age, and performance has been observed. Examples include advertisements targeting stamina and improved sexual well-being in men, hormone balance and physical appearance in women, brain health and vitality in seniors, and strength and endurance in bodybuilders.¹² DS sellers use marketing methods that target consumers in their home, where promotional material with claims about what a supplement can achieve is difficult to dispute or even scientifically investigate. A consumer simply needs to view or read the advertisement and then proceed to a store or the internet to attain it. A consumer may not realize that a DS differs from an FDA-regulated drug. Because marketing methods for drugs also occur through television, magazines, and radio, some consumers likely will not be able to distinguish a drug from a DS. Of high concern is that DS users may not report this use to their health care providers; this nondisclosure is estimated to be 24.9% for DS, with the most common reasons for nondisclosure being failure of the provider to ask and feeling that the provider did not need to know.¹³ These data confirm the importance of obtaining a complete medication history that includes use of DS as well as prescription and nonprescription drugs. The nondisclosure rate is reported to increase if the provider seems disinterested, appears judgmental of IH use, or lacks sufficient knowledge about these therapies.¹³

Legislation and Regulatory Issues

FDA regulates both finished (ready to be sold) DS products and individual dietary ingredients that are used to make DS products. Importantly, FDA regulates DS under a different set of regulations than those covering conventional foods and medications.

Dietary Supplement Health and Education Act

In 1994, the Dietary Supplement Health and Education Act (DSHEA) was approved by Congress and signed into law.¹ This act allowed FDA to regulate DS under the purview of the Center for Food Safety and Applied Nutrition. As a result, DS were excluded from the strict purity and potency standards that are

applied to prescription and nonprescription drugs by the Center for Drug Evaluation and Research. DS had to meet only the standards that applied to food preparation. Any additional standards regarding purity and potency were the sole responsibility of the manufacturer. The lack of strict good manufacturing practice standards created problems with DS content, purity, potency, consistency, and actual identity, as well as contamination, herb misidentification, and sub- and supratherapeutic effects. The lack of strict standards and limited oversight of the manufacturing process created a buyer-beware market, placing the consumer at risk and often alienating conventional health care providers to the use of IH therapies, and also led to the misconception that DS are not regulated by FDA.

Another major difference between DS and prescription and nonprescription drugs is the level of evidence required to demonstrate safety and efficacy. For prescription and nonprescription drugs, clinical trials are required to demonstrate evidence of a drug's safety and efficacy prior to its marketing. Although DS manufacturers are prohibited from marketing unsafe or ineffective products, clinical trials are not generally required to prove the safety and efficacy of DS products prior to their marketing. Some exceptions do exist such as new DS ingredients or DS with health and nutrient content claims. The DS manufacturer is responsible for the product's safety and efficacy; FDA assumes a postmarketing surveillance role and must prove that a particular DS is not safe in order to restrict its use or remove it from the market.

New Dietary Supplement Ingredients

DS ingredients that were sold in the United States prior to October 15, 1994, are not required to be reviewed for safety by FDA before they are marketed; they are assumed to be safe on the basis of a history of use in humans. For any new DS ingredient that was not on the market prior to October 15, 1994, a manufacturer must notify FDA 75 days in advance of its intent to market the product.¹ The manufacturer also must provide FDA with evidence that the DS is safe in humans when used as directed.¹ Unfortunately, a comprehensive list of DS ingredients that were sold prior to this date is not available. As a result, the decision of whether a product contains a new ingredient is left up to the manufacturer. In 2011, FDA issued comprehensive guidance that outlines specific recommendations that must be submitted in new dietary ingredient notifications. The guidance document outlines the specific materials that should be submitted to FDA and makes recommendations for the types of

safety evidence that should be submitted for new DS ingredients taken short term, long term, or intermittently. Submission of available information on genotoxicity, teratogenicity, mutagenicity, and toxicology for a dietary ingredient also is recommended.¹⁴

Current Good Manufacturing Practice

Enactment of the DSHEA required the establishment of current good manufacturing practice (cGMP) standards for the DS industry. In 2007, FDA issued a final rule on proposed changes to cGMP standards for DS.¹⁵ Some of the changes require that DS be manufactured in a quality manner without adulterants or impurities; that they be labeled accurately; and that raw materials be evaluated by the manufacturer. These changes have helped to better regulate manufacturing practices, especially with regard to setting limits on the presence of bacteria, pesticides, and heavy metals. In 2013, researchers used DNA barcoding technology to test 44 DS products marketed in both the United States and Canada; in many products that contained herbs, they found content discrepancies, herb substitution, and contaminants or use of fillers in place of active ingredients.¹⁶ These findings were of concern, because DS products marketed in the United States are required to meet cGMP standards as outlined in DSHEA. Most manufacturers achieve this requirement through their manufacturing and production processes. To address concerns about meeting cGMP standards, some manufacturers also have their DS products tested by external quality assurance programs so that their product can carry a seal of approval that verifies compliance with cGMP standards. These programs are discussed in the section “Quality Assurance Programs.”

Labeling

FDA has primary responsibility for regulating claims found on packaging, package labeling, package inserts, and other promotional materials that are distributed at the point of sale. The Federal Trade Commission (FTC) has primary responsibility for advertising claims made through print and broadcast advertisements, infomercials, catalogs, and other direct marketing materials.¹⁷ FTC requires DS claims of safety and efficacy to be supported by “competent and reliable scientific evidence.” This evidence is defined as “tests, analyses, research, studies or other evidence based on the expertise of professionals in the relevant area that have been conducted and evaluated in

an objective manner by qualified individuals, using procedures generally accepted to yield accurate and reliable results.”¹⁷ Complaints against DS advertising may be filed with FTC online.

All DS marketed in the United States must meet supplement labeling requirements.¹ The labels must list (1) the name of the product as well as the word *dietary supplement*; (2) the net quantity of contents; (3) the manufacturer’s, packer’s, or distributor’s name and place of business; and (4) directions for use. In addition, each label also must contain a supplement facts panel that describes the serving size, the list of dietary ingredients, amount per serving size, and the percent daily value, if one has been established (Figure 50–1).

FIGURE 50–1 Statutory labeling format for certain dietary supplements. (Source: Food and Drug Administration. Dietary supplement labeling guide. Available at: <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/DietarySupplements/ucm2006823.htm>. Accessed June 26, 2019.)

Plant-based DS should indicate the plant’s scientific name, or Latin binomial (i.e., genus and species), and the specific plant part used. Manufacturers may market a combination of DS ingredients as a proprietary blend. Although the individual ingredients in the proprietary blend are listed, the actual quantity of each ingredient is not disclosed. Under DSHEA, listing the total weight of the blend and the components of the blend, in order of predominance by weight, is required. Fillers, artificial colors, sweeteners, flavors, or binders also should be listed in descending order of predominance. Consistent with the trend in formulating proprietary blends, many multivitamin products are being combined with additional non-vitamin, non-mineral DS ingredients.

When a DS does not follow labeling requirements, the product is considered misbranded.¹ DS manufacturers are not allowed to make claims that their product will diagnose, cure, mitigate, treat, or prevent disease.¹ These claims would require the product to adhere to the regulations related to a drug, and the product would be subject to all the regulatory processes necessary to demonstrate safety and efficacy. Other examples of misbranding include DS that do not conform to labeling requirements; that fail to contain the name or place of business of the manufacturer, packer, or distributor; or that fail to include accurate statements regarding the quantity of the contents.

The claims for all DS products fall under one of three types: (1) health claim, (2) nutrient content claim, or (3) structure–function claim.¹⁸ Health claims and nutrient content claims require FDA approval, whereas structure–function claims do not. A manufacturer must notify FDA of the exact wording of any structure–function claim within 30 days after the product is marketed. Product labels that contain these claims also must carry a disclaimer: “This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure or prevent disease.”

Health claims describe the relationship between a food, food component, or DS ingredient and the resulting reduction in risk of a disease or health-related condition. An example of an approved health claim is claiming that a diet low in saturated fat and cholesterol that includes 25 g of soy protein daily may reduce the risk of heart disease. Nutrient content claims describe the relative amount of a nutrient or dietary substance in a product. For example, “very low sodium” means the product is required to have 35 mg or less of sodium per reference amount. Finally, a structure–function claim describes how a product may maintain the normal healthy structure or function of the body without discussing a specific disease state. A supplement manufacturer may claim that the product “supports healthy cholesterol levels” but is prohibited from indicating that the supplement may “reduce high cholesterol levels.”

Dietary Supplement and Nonprescription Drug Consumer Protection Act

One of the most important changes to the supplement industry involves the Dietary Supplement and Nonprescription Drug Consumer Protection Act (Public Law 109–462), which was signed into law on December 22, 2006.¹⁹ This law requires manufacturers, packers, or distributors of DS to submit to FDA reports of serious adverse events that are based on specific information received from the public. Serious adverse events are defined as death, a life-threatening situation, a hospitalization, a persistent or significant disability or incapacity, a congenital anomaly or birth defect, or an adverse event that, based on reasonable medical judgment, requires medical or surgical intervention to prevent such serious outcomes. Increased reporting of adverse events may better characterize the frequency and type of serious adverse events associated with DS. FDA actively evaluates trends in serious adverse events so that appropriate corrective action may be taken. Consumers and

health care providers also are encouraged to report DS-related adverse events through FDA's MedWatch adverse event reporting program (www.fda.gov/medwatch).²⁰

Production Issues

Plant Species and Parts

A health care provider should explain that herbal products typically carry two names, the common name and the Latin binomial. An example would be a product such as St. John's wort (common name), which also is known as *Hypericum perforatum* (Latin genus and species name). Some product labels may list only the Latin name, which can be confusing to a consumer who is unfamiliar with this terminology. When consumers enter a pharmacy and search for an echinacea product, they may encounter single-ingredient products that contain any of three echinacea species, *Echinacea pallida*, *Echinacea purpurea*, or *Echinacea angustifolia*; products that contain a mixture of two or all of these species; and products that contain echinacea as one of many listed supplement ingredients. In the case of echinacea, single-ingredient products involving the above-ground parts of *E. purpurea*, formulated as an alcohol extract of the fresh pressed juice, have been the most widely studied. The most recent systematic review and meta-analysis noted no reduction in cold duration for echinacea species (general to all species) in treating upper respiratory infections, but provided promising evidence, compared with placebo, in prevention of colds [risk ratio 0.77 (95% confidence interval [CI] 0.71–0.85), 9 studies].²¹

Common Product Formulations

The content of any DS is based on the raw starting material and how the material subsequently is processed or formulated. Plant-based DS such as echinacea and ginseng have greater variability in their composition than single-ingredient non-botanical products such as creatine or melatonin. This variability is caused by the chemical composition of botanical DS, which is influenced by the plant's growing conditions, the plant species, the specific plant part used, and the time of harvest.

When clinical trial data are lacking, knowing which plant species is preferred or which part of the plant should be used can be based on historical precedent. In developing countries, plant-based medicine is common, and information regarding preferred plant species, preferred plant part, and proper use is handed down from generation to generation, setting a historical precedent for use. When it comes to drug discovery, natural products are the most successful drug leads that we have as a resource. An estimated 25% of modern drugs are plant derived, and 50% are derived from natural products (e.g., plants, animals, microbes, and their derivatives).²² In developing countries, such as those in Africa, the use of plants as drugs is as high as 80%.²² The isolation of new drug compounds from natural resources is one of many reasons to extend environmental preservation and protection to biodiverse landscapes (e.g., rainforests, oceans). Use of herbs based on historical precedent also is common in the practice of midwifery. Few clinical trials exist on the use of DS in pregnant and lactating women and in children. The decision to use DS on the basis of historical precedent is something providers must discuss with their patients.

Method of Preparation

The method in which a DS is manufactured will ultimately affect its final chemical composition and potential efficacy. Some formulations may be well studied, whereas others may not have been studied at all. The most common herbal formulations that a consumer will encounter are made either directly from the fresh plant (e.g., expressed juice, tincture, tea) or from the dried plant (e.g., fluid extract or tincture, evaporated extract [capsules, tablets], tea).²³ Tinctures are most commonly prepared by combining chopped herbs with alcohol. This type of formulation should be avoided in persons taking sedating medications or medications that carry disulfiram reaction warnings. Tinctures also should be used cautiously in special populations such as infants, children, and older people. Most of the common non-plant-based DS, such as vitamins, minerals, glucosamine, creatine, coenzyme Q10, and melatonin, are manufactured as tablets or capsules; these DS represent compounds that are structurally similar to or identical to compounds naturally found in the human body.

Freshly pressed juice formulations are prepared by pressing the herb and collecting the liquid that is removed.²³ This type of preparation often takes a large amount of the herb to create a substantial portion of juice. In the case of

E. purpurea, the best-studied formulation is an alcohol extract of the freshly pressed juice.²¹ A potential advantage of the alcohol extract is that the presence of alcohol increases the product's shelf life.

Tea formulations can be prepared from the root, leaf, bark, and/or fruit of a plant. Most often they are prepared as an *infusion* by pouring boiling water over the fresh or dried leaf portions of one or more plant species and then letting the herb steep for a small amount of time.²² This process releases the water-soluble constituents into the tea. The potency is determined by the steeping time and the amount of herb used. The term *decoction* may be used when the plant parts are placed in cold water, brought to a boil, and then simmered for a period of time.²³ Common single-herb tea formulations include chamomile, ginger, peppermint, green tea, or black tea. Multi-ingredient blends that are customized to a specific person's ailment commonly are used in traditional Chinese medicine and also may be administered as teas.

Extracts are intended to concentrate the effects of an herb and can be prepared by soaking fresh or dried plant parts in alcohol, water, alcohol/water mixtures, or oil.²³ The extraction liquid is then reserved and the plant material discarded. Tinctures are fluid extracts in which alcohol is typically used as the extraction medium.²³ Chemicals that seep into the extraction liquid are specific to the solution used. If the extracted liquid is evaporated and dried, it can be formulated into tablets or capsules.²³ Extracts and tinctures may list the extraction ratio on the package label. For example, a 5:1 ratio would indicate that 5 parts of herb were used to prepare 1 part of the extract. *Ginkgo biloba* is prepared as a dried extract in tablet form. Ginkgo is typically standardized to a 50:1 extract ratio, meaning that 50 parts of the ginkgo leaf were used to prepare 1 part of the extract.²³ Garlic is available in multiple formulations, the most popular being a dried powdered extract in tablet or capsule form and an aged garlic extract. The chemical composition of the powdered extract will differ from that of the aged extract because of the differences in method of preparation. This variance in composition, in turn, may influence the efficacy of each product.

Standardization

The process of standardization is reserved primarily for plant-based DS, because herbs contain many active and inactive constituents.²³ For specific DS, standardization involves identifying specific chemicals or "markers" that

may possess therapeutic activity, isolating them, and then formulating them into a final and consistent product. Standardization can occur only if the chemical markers that contribute to the pharmacologic effect have been identified. For example, a *G. biloba* product may be standardized to contain 6% terpene lactones and 24% flavonoid glycosides, whereas a chastetree berry product may not list any standardized markers at all. The identified active chemical markers may change over time as new research is performed. For example, the active antidepressant marker for St. John's wort initially was thought to be hypericin but is now considered to be hyperforin. Bottles of St. John's wort may list one or both of these standardizations on the package label. Interestingly, no legal or regulatory definition is accepted as it relates to standardization of DS. Claiming that a product is standardized does not necessarily mean a uniform manufacturing process was used. DS verification programs (discussed later) however, may be helpful in determining compliance with package labeling and actual product composition.

Common Quality Control Issue: Adulteration

According to DSHEA, adulteration of a DS occurs when (1) the DS presents a significant or unreasonable risk of illness or injury when used in accordance with the suggested labeling, (2) the DS is a new entity and lacks adequate evidence to ensure its safety of use, (3) the DS has been declared an imminent hazard by the Department of Health and Human Services Secretary, or (4) the DS contains a dietary ingredient that is present in sufficient quantity to render the product poisonous or deleterious to human health, as described for adulterated foods in the Federal Food, Drug, and Cosmetic Act.¹ Adulteration of DS has occurred both intentionally and unintentionally. Examples of unintentional adulterants include heavy metals introduced at the time of cultivation or during the manufacturing process.²⁴ Heavy metals from environmental pollution can leach from contaminated soil into a plant as the plant grows.²⁵ In an analysis of 230 Ayurvedic medicines purchased over the internet, 21% of the Indian-manufactured medicines and 22% of the U.S.-manufactured medicines contained lead, mercury, or arsenic.²⁴ Heavy metals also may be added to traditional medicine products with the intent of promoting good health. In traditional *rasa shastra* Ayurvedic medicine, addition of heavy metals is standard practice.²⁵ In this instance, the presence of heavy metals would not be considered adulteration, because they were

added intentionally and with the goal of promoting good health. However, this practice still could lead to heavy metal toxicity for the product user if the content exceeds recommended levels for heavy metal exposure set by state or national health standards.²⁵

Intentional adulteration can occur when a manufacturer substitutes a different DS for an ingredient that is in short supply or is too expensive (e.g., economic adulteration). It also can occur when a prescription drug is added to the product to enhance its efficacy. Traditional Chinese medicines frequently have been found to contain heavy metals and undeclared drugs.²⁶ A survey of FDA Class I drug recalls performed between 2004 and 2012 found that 50% of all drug recalls involved DS products.²⁷ A Class I drug recall involves products containing a drug compound that is likely to result in serious health consequences or death.²⁷ These recalls most commonly involved products manufactured in the United States and marketed for sexual enhancement, bodybuilding, and weight loss. DS used for weight loss and energy are problematic, causing 71.8% of emergency department visits related to DS and resulting in palpitations, chest pain, or tachycardia in predominantly young patients, ages 20–34 years.²⁶ Violations of cGMP standards have been documented for nearly half of the DS manufacturing firms inspected by FDA.²⁷ The agency is addressing this issue by issuing targeted marketing about adulterated supplements to both consumers and health care providers and by creating multinational enforcement groups who target suppliers of commonly adulterated supplements.²⁷

Quality Assurance Programs

Several organizations have developed quality assurance programs to assess analytical reference standards and to certify DS composition. These programs indicate whether the DS product contents match the label contents; however, the safety or efficacy of the DS cannot be ensured. Because only a single batch is tested at any one time, these programs also do not address product quality between different batches or lots. Most quality assurance programs offer a “voluntary third party verification program” to manufacturers who pay to have their products tested. Products that pass are then allowed to carry a verification seal on the product label.

U. S. Pharmacopeia Dietary Supplement

Verification Program

In 2002, the U.S. Pharmacopeia (USP) initiated a voluntary Dietary Supplements Verification Program.²⁸ The purpose of the program is to provide consumers with a method for identifying DS that have passed rigorous standards for purity, potency, performance, and consistency in agreement with cGMP. Products earning USP certification carry a distinctive seal of approval on the product label called the “USP Verified Mark.” These products are certified to contain the listed ingredients in the indicated potency and amounts, to be bioavailable and free of contaminants, and to have been manufactured under appropriate sanitary and well-controlled conditions. As of 2019, over 100 different DS formulas representing different brands and retailers have received the USP Verified Mark. To ensure continuing adherence to quality standards, USP conducts yearly facility audits and initiates surveillance of certified products by testing products sold on store shelves. Approved products can be found at the USP website (<https://www.quality-supplements.org/verified-products>).

ConsumerLab.com

ConsumerLab.com (CL) is an independent company that tests products related to health, wellness, and nutrition, such as DS.²⁹ Products are tested on the basis of identity, purity, and consistency with the labeled ingredients. The test results are posted on CL’s website, https://www.consumerlab.com/results/brands_vitamins_supplements_list.asp, with new results available every 4–6 weeks. Manufacturers are allowed to license the CL seal of approval for a product that passes the review. To continue to carry the approval seal, a product must pass random sample testing every 12 months. The site provides free access to some information, but full access to DS testing results and product reviews requires a subscription of \$47 for 1 year or \$78 for 2 years. The specific DS products that have passed testing may not represent testing approval for the entire product line from a given DS manufacturer. The names of DS products that fail testing are available only to subscribers. The company is not affiliated with manufacturers of any DS, health, or nutrition products.

NSF International

NSF was established more than 66 years ago to standardize sanitation and

food safety requirements. Today, NSF International (<http://www.nsf.org/consumer-resources/health-beauty/supplements-vitamins/supplement-vitamin-certification>) is an independent, nonprofit organization that provides certifications of food, water, and DS quality.³⁰ This organization verifies the DS product formulation, and that it contains the labeled ingredients and that contaminants and unlisted ingredients are not present. NSF also certifies DS intended for use by athletes under the NSF Certified for Sport program. DS are screened to ensure that they contain none of the 270-plus substances banned for use by major athletic organizations nor any undeclared ingredients, including stimulants, narcotics, steroids, diuretics, beta-2 agonists, masking agents, and other substances. This program is recognized by sporting organizations including the National Football League, Major League Baseball, Professional Golfers' Association, Ladies Professional Golf Association, and the Canadian Centre for Ethics in Sports. Any DS product that meets certification standards is allowed to carry the NSF certification seal of approval on the label.

Hazards From Dietary Supplements

False Advertising and Quackery

Manufacturers who make DS health claims sometimes ignore the regulations established by FDA and FTC and market products using false or misleading claims. FTC requires all advertising to be truthful, not misleading, and based on sound scientific evidence. The weight-loss DS market is one example in which false or misleading health claims commonly are identified.³¹ Historically, this type of practice might be considered *quackery*, which implies that the person promoting use of the product knows it to be ineffective and is still promoting its use. In the case of some DS, manufacturers may believe, with or without strong clinical support, that their products are effective for a wide variety of ailments.

Consumers and providers should be wary of information found on online sites that market DS products. Some retail sites have been shown to be unreliable and may list disease claims, may fail to cite the standard disclaimer, and may lack referenced information.³² Consumers should be wary of products that contain any of the characteristics listed in [Table 50–2](#).^{31,33} In addition, consumers should consult a reliable drug information resource, as well as their health care provider, to confirm whether the health claims have a scientific

basis. Consumers and providers can go to the NIH Office of Dietary Supplements site and sign up to receive FDA and FTC press releases for products that have been identified as containing adulterants, such as prescription drugs, or for manufacturers that have been issued warnings or recalls for product quality.³¹ This online site also provides tips on how to evaluate health information on the internet.³¹ FDA also has created supplement categories that should be viewed with scrutiny because of a history of prior violations or problems.³³ These supplement categories are listed in [Table 50–3](#). A consumer or provider who wishes to file a complaint related to false advertising should contact FTC.¹⁷

TABLE 50–2 Characteristics of DS Fraudulent or Misleading Claims

- List specific disease states or allude to the product’s use for a disease usually treated with prescription drug therapy.
- State that supplement’s efficacy is similar to, or supplement can be used as an alternative to, a prescription or nonprescription drug.
- List a wide variety of unrelated clinical conditions for use.
- State only benefits and no harmful effects.
- Neglect to provide expiration date, lot number, and contact information for the manufacturer on the package label.
- Use pseudo-medical terminology such as *detoxify*, *purify*, or *improves body chemistry*.
- Use terms such as *miraculous discovery*, *revolutionary therapy*, or *breakthrough treatment*, which suggest that the product has superior efficacy to standard care.
- Suggest that the product is more expensive, because it works so well.
- Use personal testimonials in place of sound scientific evidence to support product claims.
- Promise quick relief of a health condition.
- Promote natural content as being superior to conventional medicine.
- Provide a money-back guarantee or satisfaction guarantee, but marketers of fraudulent products often change their business location.
- Make accusations that pharmaceutical drug manufacturers and health care providers are working together to defraud consumers and steer consumers away from healthier dietary supplement options.

TABLE 50–3 Categories of Supplements That FDA Cites as “Clearly Problematic”

- Treatments of potentially life-threatening diseases (e.g., HIV, cancer) or serious medical conditions such as Alzheimer disease
- Weight-loss products
- Chelation products^a
- Treatments for behavioral disorders such as attention-deficit/hyperactivity disorder or

autism

- Treatments for intellectual disability or Down syndrome
- Colloidal minerals and silver products^b
- Supplements for addiction (e.g., smoking, drinking, opiate use)
- Supplements for body building or athletic performance enhancement
- Supplements for sexual enhancement (e.g., impotence)

^a FDA has not approved any nonprescription chelation products (only prescription). Unapproved chelation products in supplement form can pose a serious risk of harm.

^b FDA has not approved any nonprescription or prescription oral silver products. Taken orally, colloidal silver may pose serious risk of harm.

Key: FDA = Food and Drug Administration; HIV = human immunodeficiency virus.

Hazards Introduced by the Consumer

Exceeding the recommended dietary allowance for a vitamin or mineral supplement or taking more of a supplement than is directed on the label can occur intentionally or accidentally. Accidental over-supplementation is more likely to occur when a consumer is taking more than one multi-ingredient product containing similar ingredients. Regardless of how it occurs, over-supplementation should be discouraged, because an adverse event may result. Overuse of some DS has serious consequences. For example, overuse of colloidal silver has led to irreversible blue-gray skin discoloration.³⁴ Overuse of calcium or vitamin D supplements over short periods may cause hypercalcemia. In addition, concern exists that excessive calcium supplementation over long periods of time may contribute to coronary artery calcification.³⁵ As mentioned previously, adverse events should be reported by consumers and health care professionals to MedWatch.²⁰ For most DS, individual case reports and postmarketing surveillance provide the best means of identifying adverse events and drug interactions. Consumers should be advised to monitor for acute adverse events for up to 2 weeks after initiating a new DS and to continue monitoring while using the product.

Product Hazards: Adverse Effects and Drug Interactions

The fact that herbal DS are derived from a natural source does not guarantee safety. Adverse effects often are linked to the pharmacology of the supplement, as was noted when products containing ephedra were removed from the market because of their association with stroke and myocardial infarction.³⁶

Some DS contain chemicals that are toxic when ingested. Pyrrolizidine alkaloids present in *Symphytum officinale* (comfrey), *Borago officinalis* (borage), *Tussilago farfara* (coltsfoot), and *Senecio aureus* (golden ragwort or life root) have been associated with case reports of hepatotoxicity.³⁷ If an adverse event is suspected, product testing is essential to rule out possible plant misidentification; adulteration with prescription or nonprescription drugs; or contamination with heavy metals, microbial contaminants, and pesticides that can occur during production.

Interactions between DS and conventional medications may have a pharmacodynamic or pharmacokinetic basis. Pharmacodynamic interactions can occur when a supplement's pharmacology is similar to or opposite that of a drug the consumer is taking. For example, both St. John's wort and L-tryptophan have been linked to case reports of serotonin syndrome in persons taking these products with prescription psychotropic drugs.^{38,39} Additive effects have occurred, or theoretically could occur, in persons combining central nervous system depressants with DS that have sedative properties, such as melatonin or valerian, or in persons combining drugs that have antithrombotic activity with DS that have antiplatelet properties, such as garlic, ginkgo, and ginger.⁴⁰ Case reports of a DS opposing the effect of a drug or adversely influencing an existing disease state have been reported infrequently in the literature. Theoretical concerns are cited as a reason to avoid DS that enhance immune system activity such as echinacea in persons who have autoimmune disorders or require immunosuppressants.⁴⁰ Finally, DS may have pharmacokinetic interactions. St. John's wort induces multiple cytochrome P450 isoenzymes, as well as the P-glycoprotein drug transporter system.⁴⁰

Communication Issues

Counseling on Dietary Supplements

The primary consideration in counseling consumers on DS is to recognize the importance of respecting the person's beliefs and values so that a trusting, nonjudgmental relationship can develop. The person must feel comfortable telling the provider about any use of DS. Providers should ask about all therapies being used, including DS, because consumers often may not disclose this information. Providers also must be able to provide recommendations regarding DS, when information is available. The risk of adverse effects versus the potential for positive effects must be considered and clearly explained. As an example, if a consumer wishes to take a DS that *has demonstrated both positive and negative outcomes in clinical trials, but lacks* documented adverse effects or drug interactions, a provider may support DS use with the caveat that it may or may not be of benefit. The consumer should be advised to monitor for perceived benefit and adverse effects. If no benefits are observed within the expected time frame, the DS should be discontinued. Providers should be less inclined to support use of a DS whose efficacy is not supported by evidence and should discourage the use of unsafe products and practices. Importantly, providers do not control access to DS, and consumers may choose to use any available DS. In many instances, providers may be in the position of educating a consumer about DS even though they believe that the product should not be used. In these situations, counseling on expectations and adverse effects is essential. For example, educating consumers on the early signs of a serious adverse effect will enable them to recognize a problem and discontinue the DS to minimize harm. Consumers always should be advised to seek medical care for serious conditions.

Health care providers should encourage consumers to read labels carefully and ask questions. Providers should be aware of the potential for confusion related to DS labels and claims, and counsel consumers in a way that lessens confusion. *Thymus* is an example of a term that might be dangerous if misunderstood. *Thymus vulgaris* is the Latin name for garden thyme. On a supplement label, "*Thymus extract*" may refer to an extract of the herbs thyme, Spanish thyme, or wild thyme, products with relatively few adverse effects when used in small doses. However, "thymus extract" may refer to a

preparation made from animal thymus gland that is marketed to enhance immune function, a product with considerable quality and safety concerns.

In addition to these broad counseling issues, the following points should be emphasized. First, providers should emphasize that most self-care with DS should be for a limited period. If a problem persists, the consumer should seek medical care. Second, consumers should inform their provider before taking DS for a condition that also is being treated with a prescription drug. Third, consumers should be informed that FDA does not require DS manufacturers to submit data demonstrating efficacy or safety before the product is marketed, unless the product contains a new dietary ingredient that was not on the market prior to October 15, 1994. Quality and consistency of DS products remain a concern but may improve with the new cGMP standards. The following points should be used in counseling consumers who wish to use a DS:

- Purchase products that have either a seal of quality on the label, acquired through a program such as the USP's Dietary Supplements Verification Program or NSF International's certification program, or that meet their content claim as assessed by ConsumerLab.com.
- Purchase from large, reputable companies. These companies have the resources to meet strict manufacturing standards, have a reputation to uphold, and are more likely to follow quality assurance procedures. Companies that also manufacture prescription or nonprescription drugs (e.g., drugstore chain brands) are more likely to have cGMP standards in place and to follow those procedures when producing DS.
- Once a quality DS has been selected, continue to use the same brand and formulation. Although this approach does not guarantee a lack of potential quality issues, given that variability between batches can occur, it does increase the likelihood of a consistent product and dose. Providers working with consumers who have not had positive results with use of a DS might consider a trial of a different brand that is appropriate for the specific symptom before determining that the supplement is ineffective for that consumer.
- Know the DS products that you are using and tell your health care provider about them to ensure your provider can identify potential safety concerns with your health conditions and potential interactions with your current medications.
- Report any adverse effects related to DS use to your health care

provider.

Additional recommendations for counseling can be found in [Table 50–4](#). Cases 50–1 and 50–2 provide examples of how to counsel consumers who wish to use DS.

TABLE 50–4 General Recommendations for Consumers

Appropriate Use

- Read all labels carefully; never take more than the recommended amount.
- Never share DS with others.
- Do not select a product that lacks dosing recommendations on the label.
- Avoid products that do not carry a lot number or expiration date.
- Discard products 1 year from the date of purchase if no other expiration date is present.
- Select products that list the manufacturer's name, address, and telephone number.
- Store products in a dry environment out of direct sunlight and away from young children and pets.

Special Groups

- Always seek the advice of a pediatrician before giving a DS to a child.
- Avoid DS if you are pregnant or breastfeeding or are trying to become pregnant.
- Ask adolescents about DS use, especially products used for weight loss, mood, sexual health, and energy.
- Speak to your health care provider if you are trying to treat a life-threatening condition, such as cancer or HIV.

Adverse Effects

- The term *natural* does not mean safe; be diligent and report any unusual experiences to your health care provider.
- If you are allergic to plants, weeds, and/or pollen, ask your provider before using a DS.
- Never take more than the amount recommended on the DS label.

Interactions

- If you are taking a prescription medication, do not take a DS or the same condition.
- When possible, avoid taking multi-ingredient preparations; select single-ingredient products that list the strength per dose.
- Do not take these products with alcohol.
- Check with your health care provider if you are taking “blood-thinning” drugs; some DS may interact with these drugs.
- Always inform your health care provider of the products you are taking; keep a list or bring them with you to your appointment.

Expectations

- Never use these products in place of proper rest and nutrition; eat a balanced diet.
- Do not expect a cure or unrealistic results; these agents are not cure-alls.
- If a claim sounds too good to be true, it probably is; use discretion when evaluating product claims.
- Keep a diary to track the effectiveness and adverse effects of DS.

Key: DS = Dietary supplements; HIV = human immunodeficiency virus.

Case 50-1

Patient Symptoms and History

Mr. McAllister is 68 years old and would like to select a joint care DS for his osteoarthritis. He was diagnosed with knee osteoarthritis 15 years ago. He describes his pain as transient: he has severe pain some weeks and no pain during other weeks. He has been using acetaminophen 500 mg every 6 hours when he is in pain as his primary care provider (PCP) recommended. His last examination showed that he has cartilage damage, and his orthopedic doctor recommended that he try glucosamine. He has high blood pressure that is stable, managed with 20 mg lisinopril daily. Mr. McAllister is an avid cyclist, walks his dog three times a day, and is in otherwise excellent health. He noticed that many different types of glucosamine products are available and would like assistance in selecting the best product.

Clinical Considerations

Mr. McAllister appears to be a great candidate for glucosamine given his history of damaged knee cartilage, a condition for which glucosamine sulfate has been shown to have some effect. Mr. McAllister is taking only lisinopril, so drug interactions with glucosamine are not likely. Mr. McAllister should select a glucosamine supplement that has been approved by one of the three DS quality assurance programs: the United States Pharmacopoeia Dietary Supplement Verification Program, ConsumerLab, or NSF International. Glucosamine products that carry a seal of approval on the label would be preferable. If the label does not bear a seal of approval, a good way to verify the quality of the product is to visit the website of a quality assurance program to verify whether the product is recommended.

Mr. McAllister also should evaluate the supplement's facts panel to help him select a product that follows appropriate DS labeling recommendations. The product he selects should list the name of the DS, its active ingredients, and the strength of each ingredient contained in each pill. The manufacturer's name and address and the recommended daily dose also should be listed. He should review and consider all of the DS ingredients listed on the label, paying special attention to the ingredients that are not necessary, included added salt (e.g., sodium chloride). This is important as increased salt intake may contribute to Mr. McAllister's high blood pressure.

If the DS label bears any statements regarding the structure or function of the body (e.g., “strengthening cartilage”) the DS product also must carry the FDA disclaimer, “This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.”

Mr. McAllister should select a glucosamine sulfate formulation, not N-acetyl glucosamine or glucosamine hydrochloride, because the sulfate formulation has been the most widely studied and has the most clinical support. He should follow the dosing recommendations on the label and keep a diary of how he is feeling while taking the supplement. He should document his knee pain, joint mobility, and stiffness over time. He also should document any side effects, including when they began and dissipated. Keeping a glucosamine diary is important, because the supplement may take several months to work. He should continue to take acetaminophen as his doctor recommended during his acute flare ups, because glucosamine is not an analgesic. Before undergoing any surgical procedures, Mr. McAllister should be instructed to let his provider know that he is taking glucosamine. Finally, Mr. McAllister should be instructed to purchase his supplements from a reputable company. This will help ensure that the company has the resources to meet strict manufacturing standards, has a reputation to uphold, and would be more likely to follow strict quality assurance procedures. Companies that also manufacture prescription and nonprescription drugs are more likely to have good manufacturing practices in place and to follow these procedures when producing DS.

Case 50–2

Patient Complaint and History

Ms. Feldman is a 67-year-old female who just came from visiting her PCP for symptoms of chest pain and forgetfulness. She was diagnosed with angina, early-onset dementia from Alzheimer disease, and constipation. Her past medical history is significant for osteopenia and lower back pain, but she is able to walk without an assistive device and to maintain a steady gait. She and her PCP are in favor of using an integrative health approach and have decided to start *Ginkgo biloba*, standardized extract, 240 mg daily, instead of an acetylcholinesterase inhibitor for her dementia. She also is picking up a new prescription for metoprolol succinate (Toprol XL 100 mg once daily) and brings a laxative called “Bowel Balance” to the counter. She routinely picks up refills of her medications for bone health (calcium and vitamin D), blood pressure (hydrochlorothiazide), and pain relief (scheduled Tylenol and as-needed Vicodin, with increased use of Vicodin over the past 2 weeks). She would like your help in selecting the best *Ginkgo biloba* DS and a laxative that meets her PCP’s recommendations. She also is seeking reassurance that the new supplement is safe to use with her prescription drugs.

You evaluate the label on the Bowel Balance laxative product and find that it is a proprietary blend of 10 ingredients with psyllium seed husks, dandelion root and leaf extract 5:1, aloe vera gel (from concentrate), ginger, and senna extract as the first five ingredients. Is this a good product for this patient? Her PCP also has recommended a standardized *G. biloba* DS. Where do you find the optimal standardization information and check for potential drug-herb

interactions?

Clinical Considerations

The ingredient listed first in a proprietary blend is present in the greatest quantity. In general, the actual amount of each ingredient in a proprietary blend is not listed, but the total weight of the blend is listed. In addition, the ingredients are listed in the order of most predominant by weight to least predominant. Evaluating the first three ingredients in a blend is a good place to start. If the ingredients listed are unfamiliar, one of the drug information resources listed in this chapter can be used to evaluate the ingredients. Psyllium is a fiber laxative; dandelion root has some digestive benefits and may help with constipation; dandelion leaf is a diuretic; aloe gel is a laxative; ginger relieves nausea or motion sickness and may help with indigestion. In light of the patient's constipation and current opiate use, it would be best to avoid use of this proprietary blend, because it is likely to have laxative and diuretic properties. Because she is using Vicodin, the best approach is recommending concomitant use of a single-ingredient stimulant laxative, such as senna, and a stool softener, along with dietary recommendations to increase intake of fiber and water. In light of her recent diagnosis of dementia, limiting the use of opiates, drugs with sedating or central nervous system actions, and anticholinergics is preferred. Using the Lexicomp natural products database, you see that a standardized extract of ginkgo biloba should be prepared from the leaf of the tree and standardized to contain 24% flavone glycosides and 6% terpene lactones. By reviewing the Supplement Facts panel of the ginkgo products in stock, you should be able to select a single-ingredient preparation that contains the correct plant species and plant part(s) and also provides evidence of this standardization. The label also should be checked for the listing of a third-party verification quality assurance program, such as U.S. Pharmacopeia Dietary Supplement Verification Process, ConsumerLab.com, or NSF International. Dosing is 120 mg orally twice daily. The database does not list any drug-herb interactions that would be significant given Ms. Feldman's medication profile. If she develops an arrhythmia in the future and is placed on warfarin or a newer oral anticoagulant, the use of ginkgo should be reassessed, because this herb has antiplatelet properties.

Considerations for Special Population Groups

This section provides a brief overview of issues regarding the use of DS by different consumers. The lack of data on safety and efficacy of DS in these groups, as well as the current regulatory issues, underscores the need for comprehensive assessment of the consumer's health status and for knowledgeable counseling.

Older Adults

Although many older adults are healthy and living independently, some may

have a significant burden of disease. The latter may have age- and disease-related physiologic declines such as impaired kidney function. Older individuals may be chronically taking multiple prescription and nonprescription drugs, making a thorough medical history essential. The potential for drug–food and drug–DS interactions, age-related functional declines, and concomitant diseases should be considered in counseling older adults about DS.

Children

Use of DS by children presents unique challenges. The central nervous system of a child may be sensitive to many drugs and chemicals, especially when they are administered at an adult dose. Little research regarding the safe and effective use of DS in children is available, making evidence-based recommendations difficult. In addition, from a practical perspective, an appropriate pediatric dosage of a DS product cannot be determined if the content of the product is in question. Finally, DS should have childproof safety closures to avoid possible accidental ingestions by young children.

Adolescents

DS use among adolescents has expanded beyond vitamin supplementation to include losing weight, building muscle, and increasing energy levels.⁴¹ Data on the safety of use of these types of DS by adolescents are limited. However, research has shown that, compared with the use of vitamins, DS used by adolescents for losing weight, building muscle, and increasing energy were associated with an almost three times greater risk for severe adverse events (e.g., emergency room visit, hospitalization, death, disability). Counseling about DS use is critical among adolescents in whom body image, peer pressure, and societal norms may be powerful drivers of DS use.

Pregnant and Lactating Women

Use of DS by a woman who is planning to become pregnant or is already pregnant presents several dilemmas. Throughout the world, herbal DS have been used to maintain health during pregnancy, prevent miscarriages, and induce labor. In the United States, concern has focused on minimizing fetal exposures to prescription and nonprescription drugs, as well as to DS. Although many natural products have been used in pregnancy, published data

on their effect on the developing embryo and fetus are sparse. As part of standard preconception care, a woman should be asked about her use of DS, especially if her nutritional status might be affected at the time of conception (e.g., folic acid intake) or her ability to become pregnant might be affected (e.g., DS effects on ovulation). The most important issue concerning DS use during pregnancy and lactation is the uncertainty about the exact content in any given product batch or brand. Currently, providers should advise women to limit their use of DS to products that have reasonable proof of safety and efficacy for use during pregnancy and lactation.

Kidney Disease

Many Americans have chronic kidney disease (CKD) caused by diseases such as diabetes. CKD presents many challenges to the safe use of many prescription and nonprescription drugs. Most commonly, the individual may be unable to eliminate the drug appropriately, potentially resulting in supratherapeutic concentrations. This effect also is true for hepatically metabolized drugs with active, renally eliminated metabolites. When a patient with CKD requires dialysis, the absorption, distribution, and hepatic metabolism of drugs also may be altered. The effects of kidney disease on DS pharmacokinetics have not been studied adequately. In addition, many herbs possess antiplatelet properties that might increase the risk of bleeding in CKD.⁴⁰

Liver Disease

The effects of liver disease on DS pharmacokinetics have not been studied adequately. Many DS products contain combination ingredients; studying and evaluating the effects of liver disease on the pharmacokinetics of combination DS present unique challenges. For this reason, DS should be avoided or used cautiously in patients with compromised liver function. Some DS products can affect the ability of the liver to metabolize other medications, which can lead to drug–DS interactions. DS products containing known hepatotoxic ingredients should be avoided. No DS have been found to be clinically effective in reversing liver disease or in preventing liver damage. However, empiric use of DS-like milk thistle and its silymarin flavonolignans (with silybin being the primary component) have been used empirically in the treatment of mushroom poisoning and in cases of nonalcoholic fatty liver disease, with some evidence of efficacy.

Surgery

A detailed preoperative history that includes questions related to DS use should be obtained from all patients undergoing surgery. If applicable, supplements that are known to affect sedation or platelet function or that might possibly affect the metabolism of anesthetic agents should be discontinued 2 weeks prior to the procedure. Any other DS that the patient is taking should be reviewed by the provider to avoid potential harm.

Reliable Information Resources

The following resources may be used for general information, ongoing research, regulatory updates and alerts, and information on DS composition. Among these, Micromedex (Alternative Medicine section), Natural Medicines, and ConsumerLab.com require a paid subscription.

Micromedex, Alternative Medicine

Micromedex, Alternative Medicine (IBM Watson Health, Greenwood Village, CO) provides drug information on all types of DS, including herbs, vitamins, minerals, Chinese medicine, homeopathy, and acupuncture. This resource provides information about DS dosing, pharmacokinetics, interactions, and clinical use, along with primary literature citations. The content undergoes extensive review and is updated quarterly. The database is searchable by DS ingredient(s) and trade name.⁴²

CARDS, NIH Office of Dietary Supplements

The Computer Access to Research on Dietary Supplements (CARDS) database contains federally funded research specific to DS. Information found in CARDS is provided from many government agencies that sponsor DS research, including but not limited to the NIH Office of Dietary Supplements. The database is searchable by DS ingredient, health outcome, study type, or names of research investigators. A record of completed and published research studies on DS is maintained within the database.⁴³

Cochrane Database of Systematic Reviews

The Cochrane Database of Systematic Reviews is accessible through PubMed and offers evidence-based analyses of DS. These reports provide detailed information on trials that were included and excluded from the analysis and on the review methodology used.⁴⁴ One advantage of this database is that statements that support or refute the use of a specific DS are expressed clearly. This database requires a subscription for access. Many providers may have difficulty understanding the style and arrangement of the information that supports the analyses. In response to this concern, each review now contains a plain language summary to help improve interpretation and to allow for translation into other languages.

ConsumerLab.com

ConsumerLab.com provides access to an encyclopedia of *Natural and Alternative Treatments*. The information in this encyclopedia is evidence based and well referenced. It is a useful resource for both consumers and health care providers.²⁹

Dietary Supplement Ingredient Database

The Dietary Supplement Ingredient Database (DSID) was created by a group of federal agencies and research organizations to estimate the levels of ingredients found in DS products. DSID provides information on analyzed levels of nutrients found in adult multivitamins and minerals used in the United States. The database is intended for use in research applications that are appropriate for conducting population-based studies on nutrient intake, as opposed to assessing individual products. The data are grouped by nutrient levels rather than by product name.⁴⁵

Dietary Supplement Label Database

The Dietary Supplement Label Database (DSLDB) was created by the National Library of Medicine and includes information from the labels of more than 76,000 DS products. DSLDB is intended to help consumers and health care professionals identify ingredients found in brand-name DS. Information in this database is based on the ingredients declared by the DS manufacturer and

includes both active and inactive ingredients. DS ingredients are linked to MedlinePlus and PubMed to allow users to investigate the dietary ingredients and evaluate related primary literature. For each DS product listed, the database provides the manufacturer's name and contact information. DSLD also provides links to fact sheets published by FDA, the NIH Office of Dietary Supplements, National Center for Complementary and Integrative Health (NCCIH), and the National Cancer Institute.⁴⁶

Lexicomp, Natural Products

The Natural Products database can be searched for more than 415 commonly used DS and is intended for use by health care providers. It is peer reviewed by an expert panel and is fully referenced to the primary literature. It contains a wide variety of information on efficacy, safety, interactions, formulations, and dosing, which can be provided as printable patient education information. The database is searchable by ingredient (both vitamin and mineral ingredients and non-vitamin and non-mineral ingredients). Brand names can be used to search for some vitamin and mineral products. Plant-based supplements are best searched using the Latin name or the scientific name.⁴⁷

MedlinePlus

MedlinePlus, published by NIH, is designed for consumers and contains information regarding diseases, conditions, and wellness. It provides consumer-friendly information about plant-based and other DS, including a summary of the science that supports an ingredient. Directories, a medical encyclopedia, and a medical dictionary are available in several languages.⁴⁸

Natural Medicines

Natural Medicines is published by the Therapeutic Research Center (Stockton, CA).⁴¹ This resource is an international research collaboration of providers from many disciplines, including those trained in Western- and Asian-based forms of care. The database provides a comprehensive listing of single-ingredient and combination DS products and their associated adverse effects, drug-supplement interactions, and more. Commercially available DS products are listed for both the United States and Canada. Recommendations for DS efficacy are graded to reflect the type and quality of the clinical evidence on

which they are based. In addition to reviews of DS, the database includes monographs on other IH modalities (e.g., acupressure, Ayurveda, biofeedback, aromatherapy), as well as a dictionary of IH terms. Each monograph has an accompanying consumer handout that is available in Spanish, French, and English.

National Center for Complementary and Integrative Health (NCCIH)

NCCIH is part of NIH and is one of the federal government's leading agencies in promoting evidence-based research on IH therapies. This online site provides information on clinical trials, opportunities for research and funding, training opportunities for IH providers, and health information on IH modalities. Links to clinical practice guidelines for vitamins and other complementary therapies also are provided.⁴⁸

Office of Dietary Supplements, National Institutes of Health

The NIH Office of Dietary Supplements is a comprehensive site for general information on DS. The online site contains information regarding health and nutrition and decision-making approaches for DS treatment options and nutrient recommendations. Importantly, the site provides evidence-based fact sheets on many DS, including vitamins and botanicals. In addition, the site provides resources for researchers of DS as well as information on DS training and career development opportunities.⁴⁹

PubMed Subset for Dietary Supplements

The NIH Office of Dietary Supplements instituted a joint project with the National Library of Medicine to create the PubMed subset for DS. This subset succeeds the International Bibliographic Information on Dietary Supplements database, which was a collaboration between the Office of Dietary Supplements and the U.S. Department of Agriculture National Agricultural Library. The subset was created to improve access to DS-related literature and incorporates journals indexed in Medline that contain this content.⁵⁰

Key Points for Dietary Supplements

- DS use is common among consumers, making it essential for all providers to be knowledgeable about the most frequently used products. This education should include information about evidenced-based resources and where to report adverse effects, drug interactions, or suspected fraudulent health claims.
- Regulation of DS under DSHEA has created a marketplace in which product safety, efficacy, and quality can vary or be unknown.
- Health care providers are in a unique position to counsel consumers on DS and should take an open, nonjudgmental, evidence-based approach.
- Obtaining a history of DS use should be part of the overall drug history.
- Counseling recommendations for DS use should include consideration of overall scientific support, historical use, specific patient groups, potential for adverse effects, and potential for interactions with other medications or medical illnesses.

Chapter 51: Natural Products

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This chapter's discussion of natural products follows an organ system approach, as outlined in [Table 51-1](#). The chapter content is based on a review of natural products of importance in pharmacy practice. Selection of products to discuss is based on whether they have evidence to support their use, are widely promoted either with or without evidence supporting their use, or present known or theoretical safety concerns.

TABLE 51-1 Chapter Supplements Grouped by Organ Systems	
System/Systemic Effect or Action	Supplement
Cardiovascular system	Coenzyme Q10
	Fish oil
	Garlic
	Red yeast rice
	Resveratrol
Central nervous system	Butterbur
	Feverfew
	Ginkgo
	Melatonin
	St. John's wort
Digestive system	Valerian
	Ginger
	Milk thistle
	Peppermint
Endocrine system	Alpha lipoic acid

System/Systemic Effect or Action	Supplement
	Cinnamon
Immune modulators	Echinacea
	Elderberry
Physical and mental performance enhancers	Eleuthero
	Asian ginseng
	Green tea
Kidney, urinary tract, and prostate	African plum
	Cranberry
	DHEA
	Saw palmetto
Musculoskeletal system	Glucosamine and chondroitin
	MSM
	SAMe
	Turmeric/curcumin
Skin conditions	Aloe vera
	Tea tree oil
Women's health	Black cohosh
	Chaste tree berry
	Evening primrose oil
	Fenugreek
	Phytoestrogens

Key: DHEA, Dehydroepiandrosterone; MSM, methylsulfonylmethane; SAMe, S-adenosyl-L-methionine.

Cardiovascular System

Coenzyme Q10

Therapeutic Uses

Consumers primarily use coenzyme Q10 (CoQ10) for cardiovascular conditions, as a general antioxidant, and for reduction of statin-associated adverse effects. It also has been investigated for use in migraine prevention, improvement of dyslipidemias, Parkinson's disease, and reduction of chemotherapy-associated adverse effects.

Physiologic Activity

Coenzyme Q10 (CoQ10 or ubiquinone) is converted to ubiquinol in the body. Ubiquinol is found in every cell, primarily in mitochondria; the greatest concentrations are in the heart, kidney, liver, and muscle.¹ As the rate-limiting cofactor in mitochondrial adenosine triphosphate (ATP) formation, CoQ10 is involved in many energy production functions and regeneration of antioxidants, such as vitamin E. Low plasma CoQ10 levels are common in migraineurs and may be predictive of mortality in patients with chronic heart failure (HF).² Statins decrease CoQ10 biosynthesis and lower its concentrations in serum, but not always in muscle tissue. The extent to which this effect occurs differs among statins.³ CoQ10 also stabilizes membranes and may have vasodilatory and inotropic effects.⁴

Dosage and Product Considerations

For heart failure, cardiomyopathy, or hypertension, a common dosage is 100 mg taken 2–3 times daily with meals to aid absorption. Dosages up to 1200 mg daily have been used safely for some neurologic conditions.⁵ The dosage to counteract depletion of CoQ10 by statins is 50–100 mg daily. For prevention of migraine, the dosage is 100 mg daily for children and 300 mg daily for adults. Products meeting United States Pharmacopeia (USP) standards are available and should be recommended.

Safety Considerations

Gastrointestinal (GI) effects from CoQ10 use may be minimized by splitting large (>100 mg) doses. Adverse effects are mild and include nausea, GI distress, anorexia, headache, irritability, and dizziness in less than 1% of patients.⁵⁻⁷ Mild increases in liver enzyme levels have been reported. CoQ10 use should be avoided in pregnancy and lactation, because safety information is lacking. Potential drug interactions with CoQ10 are listed in [Table 51-2](#).

TABLE 51-2 Examples of Dietary Supplement–Drug Interactions*

Dietary Supplement	Known Interactions/Results^a	Theoretical Interactions/Results^b
African plum (pygeum)	n/d	Potential risk of increased adverse effects when combined with finasteride or dutasteride
Alpha-lipoic acid	Increased bioavailability of valproate	SMBG recommended in patients taking antihyperglycemic drugs
		Potential chelating activity with minerals and antacids
		Possible interference with conversion of thyroxine to triiodothyronine
		Possible reduction of effectiveness of some chemotherapy agents
Black cohosh		Possible potentiation of antihypertensive agents
		May increase toxicity of doxorubicin and docetaxel
		May decrease effectiveness of cisplatin
		Avoid with hepatotoxic

Dietary Supplement	Known Interactions/Results^a	Theoretical Interactions/Results^b
		drugs
		Possible inhibition of CYP450 and CYP2D6
Butterbur		Possible interaction with anticholinergic drugs or antimigraine medications
		Avoid with known inducers of CYP3A4; possible pyrrolizidine increases
Chasteberry		Possible interference with HT or OCPs
		Possible interaction with antipsychotics, dopamine agonists and antagonists, and metoclopramide due to dopaminergic activity
Cinnamon		Additive effects with antihyperglycemic agents
		Avoid large doses in combination with hepatotoxic agents due to coumarin content
Chondroitin		Possible increased risk of bleeding if taken with antithrombotic agents; may increase INR in combination with warfarin
Coenzyme Q10		Possible vitamin K-like procoagulant effects if taken with warfarin; monitor INR initially
		Possible additive effects with antihypertensive

Dietary Supplement	Known Interactions/Results^a	Theoretical Interactions/Results^b
		agents
Cranberry	Atorvastatin: increased adverse effects from concomitant daily cranberry juice	Possible increased levels of CYP3A4 substrates
		Possible increased INR and risk of bleeding in people taking warfarin
		Possible CYP2C9 inhibition
		May alter excretion of weakly alkaline drugs or neutralize effects of antacids
DHEA	Triazolam: increased blood levels	Interference with hormonal or antihormonal therapies
	Antidepressants; increased risk of mania	May increase risk of thromboembolism with OCPs
		Possible increased levels of CYP3A4 substrates
		Possible reduction of tuberculosis vaccine efficacy (animal data)
Echinacea	Caffeine: increased levels	Possible interaction with immunomodulating therapies.
		Caution with CYP3A4 substrates that have low oral bioavailability: verapamil, cyclosporine, tacrolimus.
		Effects on CYP1A2, CYP2C9, or CYP3A4 are likely to be clinically

Dietary Supplement	Known Interactions/Results^a	Theoretical Interactions/Results^b
		insignificant. Effects on hepatic and intestinal CYP3A4 can be opposing.
Elderberry		Possible decrease in effects of immunosuppressant agents due to immunostimulation
		Possible additive effects with antihypertensive and antihyperglycemic agents; increased monitoring recommended
Eleuthero ("Siberian ginseng")	Digoxin: possible false elevation in plasma levels (assay dependent)	SMBG recommended in patients taking antihyperglycemic agents due to unpredictable effects.
	Caffeine: increased CNS stimulation	Possible inhibition of CYP1A2 and CYP2C9
		Possible inhibition of P-glycoprotein
		Possible additive effects with antithrombotic agents
Evening primrose oil	Lopinavir: increased levels (case report)	Antithrombotic agents: possible additive effects
		Possible increased risk of seizure possible with phenothiazines
		Potential additive effects to antihypertensives
Fenugreek		Antithrombotic agents: possible additive effects

Dietary Supplement	Known Interactions/Results^a	Theoretical Interactions/Results^b
		Avoid with antihyperglycemic drugs due to additive effects.
Feverfew		Possible additive effects if taken with other antithrombotic agents or herbs
		Possible inhibition of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4
Fish oil		Antithrombotic agents: possible additive effects primarily at dosages >4 g daily
		Antihypertensives: possible additive effects
Garlic	Warfarin: increased INR in case reports	Contradictory evidence regarding induction of drugs metabolized through CYP3A4 and CYP2D6
	Saquinavir: 50% decrease in levels	
	OCPs: decreased effectiveness	Possible inhibition of CYP2E1
	Isoniazid: significantly decreased levels	
Ginger	Antithrombotic agents: possible additive effect	Avoid with antihyperglycemic drugs because of additive effects.
	Nifedipine: decreased platelet aggregation	Possible increased effects of warfarin; monitor INR
Ginkgo	Antithrombotic agents: possible additive effect (contradictory evidence)	Excessive ingestion associated with seizures;

Dietary Supplement	Known Interactions/Results^a	Theoretical Interactions/Results^b
		avoid in patients with a history of seizures or on drugs that may lower seizure threshold
	Atorvastatin: decreased clearance, though efficacy does not seem to be decreased	Potential additive effects with antihypertensive drugs, although paradoxical hypertension has been reported with HCTZ
	Efavirenz: decreased levels	Possible reduction concentrations of ritonavir, lansoprazole, and tolbutamide
	Omeprazole: decreased levels	
	Trazodone: case report of coma in patient taking low-dose trazodone	
Ginseng (<i>Panax ginseng</i>)	Glucose-lowering drugs: possible lowered BG levels in type 2 diabetes mellitus; SMBG levels required	Unpredictable effects on concurrent antithrombotic agents
		Possible interference with antipsychotics and immunosuppressants
	Phenelzine: possible headache, tremor, and mania in case report	Possible inhibition of CYP1A1, CYP2D6
	Imatinib: increased toxicity	Unpredictable effects on metabolism of CYP3A4 substrates
		Possible additive effects when used with medications that prolong the QT interval
Glucosamine	Warfarin: increased bleeding risk in individuals with variant CYP2C9 alleles	SMBG recommended for first few days of use in patients taking

Dietary Supplement	Known Interactions/Results^a	Theoretical Interactions/Results^b
		antihyperglycemic drugs
		Coadministration with acetaminophen may decrease pain control
Green tea	Decongestants, amphetamines: additive stimulant effects	Possible antagonism of warfarin's effect
	Cimetidine: increased effects of caffeine content	Possible antagonism of concurrent sedatives related to caffeine content
	Nadolol: clinically significant reductions in drug levels	Possible reduction in serum folate levels
Melatonin	Nifedipine: reduced delivery by GITS via unknown mechanism	Caffeine or OCP use: various effects on melatonin levels
		Verapamil may decrease melatonin
	Fluvoxamine, MAOIs, and tricyclic antidepressants: increase melatonin	Possible interaction with immunosuppressant drugs related to immunostimulating properties
	BZDPs, sodium valproate, and beta blockers: decrease nighttime levels	May increase seizures due to inhibition of anticonvulsant effects
Milk thistle		Inhibition of CYP2C9, CYP2D6, and CYP3A4 is unlikely; evidence is contradictory
		Possible additional decreases in blood glucose; use caution with antidiabetic medications
		Possible inhibition of

Dietary Supplement	Known Interactions/Results^a	Theoretical Interactions/Results^b
		drugs that undergo glucuronidation
Peppermint	Decreased absorption of iron salts	Possible inhibition of CYP3A4, CYP2C9, and CYP2C19
	Antacids or other drugs increasing gastric pH: early dissolution of enteric-coated capsules	
Phytoestrogens (red clover, others)		Red clover-based products: possible increased risk of bleeding in patients taking antithrombotic agents
		Phytoestrogens: possible interference with antitumor effects of tamoxifen
Red yeast rice	Additive activity and risk of adverse effects when used with statins	CYP3A4 inhibitors: possible increased levels and adverse effects
		Gemfibrozil: possible increased adverse effects
SAMe	Antidepressants and 5-HT ₁ agonists: greatly increased risk of serotonin syndrome	Risk of additive adverse effects with monoamine oxidase inhibitors
		Risk of decreased effects of levodopa due to methylation
		Avoid concomitant use with corticosteroids due to possible effects on glucocorticoid concentrations
Saw palmetto		Potential interaction with hormonal or antihormonal therapies in

Dietary Supplement	Known Interactions/Results^a	Theoretical Interactions/Results^b
		men and women
		Possible additive effects when used with antithrombotic agents
St. John's wort	CYP3A4 substrates: significantly decreased drug levels and effects (e.g., alprazolam, amitriptyline, atorvastatin, erythromycin, finasteride, imatinib, irinotecan, methadone, nifedipine, simvastatin, tacrolimus, verapamil, voriconazole, warfarin, zolpidem)	Possible increased risk of serotonin syndrome if taken with 5-HT ₁ agonists, dextromethorphan, meperidine, and tramadol
		Digoxin: decreased intestinal absorption, decreased levels
	Antidepressants: increased risk of serotonin syndromes	Possible decreased levels and effect of amiodarone, theophylline, and proton pump inhibitors
	Cyclosporine: decreased blood levels of immunosuppressant leading to transplant graft rejection	Monitoring for fexofenadine toxicity recommended if taken concomitantly
	OCPs and HT: decreased activity	Morphine: increased narcotic-induced sleep time in animal studies
	Protease inhibitors, nonnucleoside reverse transcriptase inhibitors, and nonstructural protein 5A or 5B inhibitors: decreased serum levels	Use with other photosensitizing agents contraindicated
Turmeric	Sulfasalazine and tacrolimus: significantly increased blood levels	Possible increased effects with antithrombotic agents
	Glyburide: decreased post-prandial glucose	Possible P-glycoprotein inhibition
Valerian		Possible increased sedative effect if taken with alcohol or other CNS

Dietary Supplement	Known Interactions/Results^a	Theoretical Interactions/Results^b
		depressants (i.e., BZDPs)
		Possible inhibition of CYP3A4
		Possible decreased metabolism of UGT1A1 and UGT2B7 substrate drugs

* Table is not all-inclusive. Additional resources should be consulted for clinical use.

^a Based on human studies and/or validated case reports.

^b Extrapolated from animal or in vitro studies.

Key: BG = Blood glucose; BZDP = benzodiazepine; CNS = central nervous system; CYP = cytochrome P450; DHEA = dehydroepiandrosterone; GITS = gastrointestinal therapeutic system; HCA = hydroxycitric acid; HCTZ = hydrochlorothiazide; HT = hormone therapy; 5-HT₁ = 5-hydroxytryptamine; INR = international normalized ratio; MAOI = monoamine oxidase inhibitor; OCP = oral contraceptive pill; SAME = S-adenosyl-l-methionine; SMBG = self-monitoring of blood glucose; SSRI = selective serotonin reuptake inhibitor; UGT = UDP-glucuronosyltransferase

Summary of Clinical Evidence

Evidence for CoQ10 in HF is contradictory. Studies have shown excellent results on cardiovascular health markers such as endothelial function and C-reactive protein levels, whereas trials examining symptoms or ejection fraction have demonstrated improvements or no effects when CoQ10 was added to standard therapies.^{8,9}

One large, well-designed 2-year study examined short- and long-term effects in patients with HF taking 300 mg daily CoQ10 or placebo.¹⁰ The groups had similar improvements in symptoms and function at 16 weeks; however at 106 weeks, 58% of patients taking CoQ10 had improved at least one New York Heart Association (NYHA) class compared with 45% of patients taking placebo. At 106 weeks, risk of cardiovascular events was reduced by 43% in the CoQ10

group compared with placebo, as was the risk of cardiovascular death at 9% versus 16%.

Whether supplemental CoQ10 can reduce adverse effects associated with statins remains controversial. Some studies support CoQ10's effects to reverse statin-associated adverse effects with or without statin discontinuation.^{11,12} A 2015 meta-analysis of six trials concluded that myalgia or other adverse effects were not reduced significantly; an additional trial in patients with confirmed simvastatin-induced statin myopathy found no differences between CoQ10 600 mg daily and placebo after 8 weeks.¹³ In a 2019 meta-analysis specifically focused on fatigue associated with multiple conditions, CoQ10 was shown to be beneficial for statin- and fibromyalgia-related fatigue, but not fatigue from other causes.¹⁴ Genetic differences may contribute to the variable responses to CoQ10 treatment.¹⁵

Although its true efficacy is unknown, CoQ10's favorable adverse effect profile does support a trial of adjunctive use in HF or for reduction of statin-induced adverse effects. Patients should discuss these indications, as well as the dose and duration for the trial period, with the health care provider before they add CoQ10 to the standard treatment regimen.

Fish Oil

Fish oil is a source of omega-3 fatty acids, primarily docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA).

Therapeutic Uses

Fish oil is used to lower triglyceride (TG) levels, improve cardiac health, aid in the treatment of depression, and relieve inflammatory conditions such as rheumatoid arthritis and psoriasis. American diets tend to be low in omega-3 fatty acids and high in omega-6 fatty acids. The American Heart Association recommends a minimum intake of a serving of fatty fish twice weekly for heart health.¹⁶ Consumers who do not eat fish can take fish oil supplements or plant-based omega-3 supplements to improve the omega-3:omega-6 ratio; however, less clinical evidence is available for plant-based supplements.

Physiologic Activity

Omega-3 fatty acids may decrease intestinal absorption of cholesterol and inhibit enzymes involved in synthesis, excretion, and degradation of very low-density lipoproteins, thereby decreasing levels of other lipoproteins, including low-density lipoproteins.¹⁷ The mechanism of hypotriglyceridemic action through peroxisome proliferator-activated receptors also may be responsible for improvements in glucose concentrations and insulin resistance.¹⁸ Hypotensive effects may result from decreased vasoconstriction triggered by angiotensin II.¹⁹

Intake of EPA and DHA in fish oil influences the production and concentrations of inflammatory response cytokines. Competitive inhibition of arachidonic acid decreases production of thromboxane A₂ and leukotriene B₄, whereas effects at another part of the production cascade increase levels of thromboxane A₃ and prostaglandin E₃. Fish oil's mechanism of action can be summarized as increasing levels of noninflammatory cytokines while decreasing proinflammatory cytokine levels. Plaque inflammation is decreased through the chemical mediators, resolvins, and protectins, which are derived solely from omega-3 fatty acids.²⁰

Dosage and Product Considerations

The usual recommendation for balancing the omega-3 and omega-6 ratio is 1–2 g daily of fish oil. For hyperlipidemia, dosages of 2–4 g daily in divided doses are common, but trials have used higher doses that may be considered for individual patients to reach desired lipid goals. Most studies have used products with an EPA:DHA ratio of 1.2:1 or 1.5:1. The actual quantities of EPA and DHA may not equal the stated total dose per capsule because of added excipients and other components; however, quantities of these ingredients in high-quality products will be close to the stated dose. For example, a “1 gram fish oil” product labeled to contain “480 mg EPA and 370 mg DHA” per capsule would be within the acceptable ratios, whereas a “1 gram fish oil” product with “250 mg EPA and 180 mg DHA” per capsule would not. For vegetarian/vegan patients, DHA and DHA/EPA products made from algae are available. DHA/EPA quantities may be lower though, so the total dosage of the algal oil may need to be higher.

Enteric-coated capsules taken with meals or at bedtime are recommended to

minimize the common “fish burp” effect. Anecdotally, some patients have success with freezing capsules. Data on mercury and other toxin levels in fish have increased concerns about the quality of fish oil supplements. Because mercury is insoluble in oil, it collects primarily in flesh, whereas most of the ingested fish oil is extracted from the skin. Tests of mercury levels in fish oil supplements showed no or barely detectable concentrations of mercury.²¹ However, dioxin and pesticides can accumulate in the oil. To limit exposure to these toxins, patients should be advised to purchase high-quality products that meet USP standards.²²

Supplements made from the more expensive krill oil often are marketed as superior to fish oil. Although both types of oil have demonstrated similar effects in animal studies and some human studies, human clinical trials are needed before a recommendation can be made.²³

Safety Considerations

In general, fish oil products are safe; the most common adverse effects are belching with fishy halitosis and GI distress. Because fish oil does decrease platelet aggregation in healthy individuals, cautions to stop its use before surgical procedures are common. However, a recent systemic review found no increased risk of bleeding in patients undergoing surgery and noted that some trials demonstrated a decreased need for postoperative red blood cell transfusions.²⁴ Additionally, trial evidence has demonstrated that even higher doses, up to 6.9 g daily in combination with aspirin and heparin or with warfarin, did not result in an increased risk of bleeding events.^{20,24}

Summary of Clinical Evidence

Evidence discussed in this chapter pertains to dietary supplement forms of fish oil; study results for prescription omega-3 supplements, such as Vascepa, or other sources of omega-3s, such as flax oil, cannot be applied to these products. Fish oil’s greatest effect is on TG levels. A meta-analysis of 38 trials found dietary fish oil intake of 4 g daily or greater to be associated with reductions of 9%–26% in TG levels, whereas 1–5 g daily of fish oil supplements were associated with reductions of 4%–51%.²⁵ The Agency for Healthcare Research and Quality (AHRQ) conducted an evidence review of omega-3 fatty acids in 2016. Study data showed that the strength of evidence for fish oil’s ability to lower TG levels was high (–24 mg/dL, 95% CI –31 to –18). The data also

showed modest increases in high density lipoprotein (HDL) (0.9 mg/dL, 95% CI 0.2–1.6) and reduction of the total cholesterol (TC)/HDL ratio (–0.17, 95% CI –0.26 to –0.09) in patients with lower CVD risks.²⁶ Data for the effects of omega-3 fatty acids on LDL levels are variable, with some studies noting small increases and others noting small decreases.^{25–27}

After significant cardiovascular risk reduction was noted in the landmark GISSI-Prevenzione trial, many studies evaluated cardiovascular measures. Disease management has changed considerably since that time, which may explain the conflicting results reported in newer trials. Over the last decade, meta-analyses of fish oil trials have come to conflicting conclusions regarding its cardiovascular risk reduction.²⁸ Several trials have demonstrated increased lipid lowering when fish oil was added to statin therapy, and one large ($N = 18,645$) study demonstrated a 53% reduction in heart disease in patients with elevated TG and low HDL.²⁹ Other studies found no additional benefit either for decreasing lipid levels or for reducing cardiovascular risk.³⁰ One in-depth analysis suggests that fish oil may reduce cardiovascular risk in only patients who have low omega-3 fatty acid levels, and that no additional protective effects occur in patients already taking statins. These findings may be related to competitive interference caused by increased levels of arachidonic acid.³⁰

Patients on hemodialysis experience an increased risk of thrombosis due to arteriovenous (AV) grafts for vascular access. A meta-analysis of 13 controlled trials using doses of 1.3–6 g daily of fish oil in these patients revealed a decreased risk of AV graft thrombosis (RR 0.71, 95% CI 0.52–0.97, $P = 0.03$) and a decreased risk of cardiovascular events (RR 0.41, 95% CI 0.26–0.66, $P = 0.0002$).³¹

Fish oil may be safely recommended to aid in triglyceride reduction and to increase omega-3 dietary intake. Patients who are interested in fish oil for reduction of cardiovascular risk should be counseled that the potential benefit may be low and is affected by many factors, including concomitant statin therapy.

Garlic

Therapeutic Uses

Garlic products derived from dried or fresh bulbs of *Allium sativum* are promoted for treating hyperlipidemia, hypertension, type 2 diabetes mellitus,

as well as for increasing immune function and preventing of cancers.

Physiologic Activity

Garlic bulbs contain the odorless sulfur-containing amino acid derivative alliin (S-allyl-L-cysteine sulfoxide). When crushed, the enzyme allinase is released and converts alliin to pungent allicin, the main component of garlic's volatile oil. Allicin is used as a product quality marker but is not the only active compound; other substances such as S-allylcysteine (SAC) also exert pharmacologic effects. In animal and in vitro models, garlic has been shown to possess antiplatelet and anti-infective properties. Garlic's ability to prevent lipid oxidation may be as important to cardiovascular health as its hypolipidemic and antihypertensive activity.³² Garlic increases levels of the vasodilator hydrogen sulfide, enhances nitric oxide production, and may inhibit angiotensin-converting enzyme.³³

Dosage and Product Considerations

Differences in dosage forms may be responsible for varied outcomes in clinical trials. Patients should use only products similar to those used in clinical trials: either powdered garlic standardized to allicin content of 1%–1.6% providing 3–5 mg allicin per day or aged garlic extracts (AGE) containing at least 1.2 mg SAC should be recommended.³⁴ Enteric-coated products may help to decrease “garlic breath.”

Safety Considerations

Although well tolerated, garlic may cause GI adverse effects including nausea, reflux, vomiting, and heartburn, especially with higher dosages or in the first week of therapy. Garlic breath and body odor also may occur. Allergic reactions have been reported rarely.

Garlic should be stopped 10–14 days prior to surgical procedures to avoid excessive bleeding. Patients taking antithrombotic agents should use garlic supplements with caution because of the potential risk of bleeding, which may vary with the type of product; however, dietary amounts of garlic do not affect platelet function.^{35,36}

Garlic's effects on cytochrome (CYP) P450 isoenzymes are unclear, but enzyme

induction is possible; drug profiles should be reviewed for potentially severe interactions before garlic is initiated. (See [Table 51–2](#) for potential drug interactions.)

Summary of Clinical Evidence

A 2013 meta-analysis of 37 trials concluded that garlic reduces TC by 15 mg/dL, which may be clinically meaningful for only patients who need small reductions. Studies of 13–52 weeks in duration reported reductions up to 19.63 mg/dL; decreases in LDL levels were more modest at 7–9 mg/dL.³⁴ A subgroup analysis suggests that aged garlic extracts may have more health benefits than garlic powder products; garlic oil and raw garlic have shown little beneficial effect.³⁴ Overall, patients with TC levels higher than 200 mg/dL experienced greater reductions.

With respect to hypertension, a 2016 meta-analysis of nine trials concluded that in hypertensive patients, garlic reduces systolic blood pressure (SBP) and diastolic blood pressure (DBP) by a mean of 8.7 and 6.1 mm Hg, respectively, compared with placebo.³⁷ However, normotensive individuals had SBP and DBP reductions of 5.1 and 2.5 mm Hg, respectively.³⁷ A 2015 meta-analysis concluded that garlic effected SBP and DBP mean reductions of 9.36 and 3.82 mm Hg, respectively; the authors stated the reductions were similar to those in a meta-analysis of 354 short-term studies of prescription antihypertensive agents.^{38,39}

A 2016 randomized controlled trial evaluated blood pressure response in 88 individuals who had hypertension and were receiving 1.2 g daily of AGE for 12 weeks.⁴⁰ Responders were classified as those with reductions of more than 3% in SBP and DBP. The mean SBP reduction in all participants was 5 mm Hg ($P = 0.016$ compared with placebo); however, in the responder subgroup, the mean SBP reduction was 11.5 mm Hg, with a 6.3 mm Hg decline in DBP ($P < 0.001$). Overall, current evidence does support garlic as a suitable option for patients with mild hypertension, mild hypercholesterolemia, or both; however, long-term outcome studies are not available.

Red Yeast Rice

Monascus purpureus, a yeast that grows on fermented rice and gives Peking duck its red hue, is used in traditional Chinese medicine.

Therapeutic Uses

Red yeast rice is used to lower lipid concentrations.

Physiologic Activity

Red yeast rice contains multiple components, including several closely related compounds termed *monacolins*. Monocolin K, which is structurally identical to lovastatin, is the most important monacolin. The standard dosing for most red yeast rice products usually contains less than 5 mg daily of monacolin K. Therefore, it cannot be solely responsible for the extent of lipid-lowering effects reported in clinical trials. Additional mechanisms are probable, including increased bile acid excretion.

Dosage and Product Considerations

For hyperlipidemia, the dosage of red yeast rice is 1.2–2.4 g daily in 2 doses. In the United States, certain red yeast rice products have been declared illegal, because they contained an “unauthorized drug.”⁴¹ As a result, many manufacturers no longer ensure products contain a standardized amount of monacolin K, making selection of a high-quality, effective product more difficult.⁴¹ study of 28 supplements found that monacolin K content ranged from 0.09–5.48 mg per 1200 mg of red yeast rice.⁴²

Safety Considerations

Although red yeast rice usually is well tolerated, adverse effects such as allergic reactions, headache, and mild GI symptoms that include bloating, flatulence, and heartburn can occur. A 2019 systematic review and meta-analysis examined red yeast rice safety in trials that included 8535 patients. No increase in musculoskeletal adverse events were noted, and, compared with controls, the risks of non-musculoskeletal adverse events and serious adverse events were reduced: OR = 0.59 (95% CI 0.50–0.69) vs OR = 0.54 (95% CI 0.46–0.64), respectively.⁴³ Monitoring liver function 1–2 months after starting red yeast rice, and annually thereafter, is recommended because of reported increased levels of liver function enzymes.⁴¹ Patients with daily alcohol intake of more than 2 drinks should not use red yeast rice because of the potential risk of increased hepatotoxicity. One case report exists of erectile dysfunction that resolved after discontinuation of the red yeast rice supplement.⁴⁴ Any use of

red yeast rice is contraindicated in pregnancy.⁴⁵

The *M. purpureus* yeast also can generate citrinin, a nephrotoxin, during fermentation.⁴⁶ Only red yeast rice brands assured to be free of citrinin should be used; patients with kidney disease should not use red yeast rice.

At least three studies have found that red yeast rice can be used safely in patients unable to take statins. Rare cases of rhabdomyolysis associated with red yeast rice have been reported; these cases may be associated with products of higher monacolin K content.^{47–49} For patients with previous statin-induced myalgia, increased monitoring at the start of red yeast rice therapy is appropriate.

Summary of Clinical Evidence

Multiple studies have demonstrated that red yeast rice lowers lipid concentrations. A 2015 meta-analysis reported a mean reduction of 39.44 mg/dL in LDL compared with placebo; the authors noted that the reduction was similar to the LDL-lowering effects of statin use.⁵⁰ A 2016 systematic review of 10 trials of red yeast rice versus simvastatin examined the effects of both treatments on TC, LDL, HDL, and TG. Simvastatin and red yeast rice were found to have similar effects on all lipid measures.⁵¹ A 2019 study in 50 patients of 3 month's duration compared a monacolin K-rich red yeast rice supplement and a gamma aminobutyric acid (GABA)-rich supplement with placebo.⁵² Reductions of TC and LDL levels in only the monacolin K-rich group were significant and also were similar to reductions observed in previous trials, –44.5 mg/dL ($P < 0.001$) and –31 mg/dL ($P < 0.001$), respectively. TG reductions were greater, although not significantly, in the GABA-rich group, and no changes were seen in HDL in any group.

Whether red yeast rice possesses benefits for cardiovascular risk reduction similar to statins remains unknown.

Resveratrol

Therapeutic Uses

Resveratrol is a polyphenol derived from grapes and berries. Interest in its properties resulted from epidemiologic research that found a cardioprotective

effect associated with red wine intake. Higher dietary intake also has been associated with lower lipid levels, blood pressure, glucose, and heart rate.⁵³

Physiologic Activity

Resveratrol is an antioxidant with anti-inflammatory activity; in vitro and animal studies have demonstrated its antineoplastic effects in multiple types of cancers.⁵⁴ Effects in cardiovascular diseases include decreased SBP and DPB, as well as improved vasodilation and vascular relaxation. Multiple animal species models have shown reduction of atherosclerosis development, attenuation of myocardial injury, and reduction of cardiac remodeling ischemia or infarction. The mechanisms of these effects are multiple and include increased endothelial nitric oxide synthesis, reduced messenger RNA expression of proinflammatory molecules such as tumor necrosis factor α (TNF α), and decreased expression of vascular cell adhesion molecule 1.⁵⁴ Use of resveratrol in humans improved cardiovascular risk markers such as lipid levels, apolipoprotein A-1, TNF α , C-reactive protein, and interleukin-10 (IL-10).⁵⁵ Resveratrol also increases insulin sensitivity; animal studies have noted improvements in glucose, fructosamine, and hemoglobin A1C levels.⁵⁶

Dosage and Product Considerations

Although about 75% of a resveratrol is absorbed, bioavailability is actually <1%, because of hepatic and intestinal metabolism.⁵⁷ Trials have used dosages of 25–4000 mg daily. The optimum dosage has not been determined.

Safety Considerations

Resveratrol is well tolerated. Clinical trial subjects have reported mild GI symptoms of loose stools with increased frequency for the first month of treatment.⁵⁸ Patients on peritoneal dialysis have reported increased frequency of GI symptoms, headache, and muscle cramps. Animal data have not reported negative pregnancy outcomes; use in pregnant women is not recommended, because data for resveratrol's effects in humans are lacking.⁵⁹

Summary of Clinical Evidence

A meta-analysis of 17 trials examined resveratrol's effects on blood pressure.⁵⁸ Researchers noted heterogeneity in trial results. Overall, the mean differences

seen for SBP, mean arterial pressure, and pulse pressure were -2.468 , -1.346 , and -0.855 , respectively; these results did not reach statistical significance ($P = 0.116$, 0.07 , 0.449 , respectively). In most of the trials, DBP showed little or no change. A subgroup analysis found that patients with diabetes were more likely to experience SBP-lowering effects with resveratrol treatment (-8.8 mm Hg, 95% CI -12.5 to -5 , $P < 0.001$). The mean difference in SBP reductions in patients taking dosages of 300 mg daily or more was -2.5 mm Hg (95% CI -4.9 to -0.04 , $P < 0.047$). The authors concluded that further research into resveratrol's benefits on hypertension is warranted. The clinical data do not yet include long-term outcomes such as cardiovascular morbidity or mortality.

Central Nervous System

Butterbur

Petasites hybridus, also known as butterbur, is native to marshy areas in northern Asia, Europe, and parts of North America. It is a member of the Asteraceae/Compositae family, which includes a wide range of flower plants, such as daisies and ragweed. Many natural products discussed in this chapter belong to this family.

Therapeutic Uses

Butterbur is used to prevent migraines and treat allergic rhinitis and asthma.

Physiologic Activity

Petasin and isopetasin are isolated from butterbur's rhizomes, roots, and leaves. Extracts also contain volatile oils, tannins, flavonoids, and pyrrolizidine alkaloids (PAs). Petasin may reduce spasms in smooth muscle and vascular walls and may also inhibit leukotriene synthesis. Isopetasin decreases prostaglandin synthesis, thereby reducing inflammation. Both compounds have an affinity for cerebral blood vessels.⁶⁰

Dosage and Product Considerations

For migraine prevention, studies have used standardized extracts of butterbur containing a minimum of petasin 7.5 mg and isopetasin 7.5 mg per 50 mg

tablet or capsule. Dosages of standardized butterbur ranging from 50 to 75 mg twice daily are taken for 4–6 months and then tapered until the incidence of migraines increases. The maximum study duration has been 12–16 weeks.⁶⁰ Standardized petasin (Ze 339) 8–16 mg has been administered 3–4 times daily for allergic rhinitis.^{61,62}

Safety Considerations

Butterbur is well tolerated with minor GI symptoms most commonly reported, followed by skin changes and dizziness.⁶⁰ Butterbur extracts contain the toxic compounds PAs and their N-oxides that can cause serious hepatotoxicity and carcinogenesis. Products labeled as PA-free should be recommended.⁶³ Patients with an allergy to ragweed and related plants in the Asteraceae/Compositae family should avoid butterbur. Its use also should be avoided during pregnancy and lactation because of the potential for hepatotoxicity.

Summary of Clinical Evidence

The American Academy of Neurology and the American Headache Society considers butterbur effective for the prevention of migraine, with an evidence level of A based on two randomized controlled trials.⁶⁴ Studies including children and adolescents also have shown positive results in lower-quality studies.⁶⁵ In patients with seasonal allergic rhinitis, short-term studies of butterbur suggest efficacy similar to that of cetirizine and fexofenadine.^{61,62}

Feverfew

Tanacetum parthenium, also known as feverfew, is a member of the Asteraceae/Compositae family. The plant is native to the Balkans and is now found throughout the world.

Therapeutic Uses

Feverfew is used to prevent migraines and to treat dysmenorrhea, arthritis, and psoriasis.

Physiologic Activity

The activity of feverfew for migraine prevention involves multiple mechanisms.

Parthenolide, a sesquiterpene lactone, is the most abundant and biologically active component; it likely contributes anti-inflammatory benefits. Other active components include flavonoids, volatile oils, and additional sesquiterpene lactones. Feverfew may have effects on prostaglandin synthesis, platelet aggregation, serotonin release, histamine release, and vascular smooth muscle contraction.⁶⁶

Dosage and Product Considerations

Studies have used feverfew leaf 50–100 mg daily in divided doses or 6.25 mg carbon dioxide–standardized extract (MIG-99) of 0.2%–0.35% of parthenolide 2–3 times daily.⁶⁷ Standardization of a product to its parthenolide content has not appeared to be necessary, because the content has varied throughout studies. Feverfew must be taken continuously for migraine prophylaxis and is not effective for treatment of acute migraine attacks.

Safety Considerations

GI adverse effects may result from ingestion of feverfew. Oral ulcers can occur from chewing fresh leaves. Post-feverfew syndrome has been reported after abrupt withdrawal from chronic use, resulting in anxiety, headaches, insomnia, and muscle stiffness. Patients who are allergic to plants in the Asteraceae/Compositae family should avoid use of feverfew, as should women who are pregnant or breastfeeding.⁶⁶ Possible antiplatelet effects have been identified, so patients taking antithrombotic agents should use feverfew with caution.^{66,68}

Summary of Clinical Evidence

A Cochrane review found insufficient evidence to support feverfew for the prevention of migraines, although an update included a well-designed study of MIG-99 that showed an overall decrease of 0.6 migraines per month compared with placebo.⁶⁷ The long-term safety and efficacy have not been established, and the American Academy of Neurology and the American Headache Society consider MIG-99 probably effective for prevention of migraine, with an evidence level of B.⁶⁴ Preliminary evidence of a fixed combination of feverfew 100 mg, coQ10 100 mg, and magnesium 112.5 mg taken daily has shown benefit in migraine symptoms.⁶⁹

A Word About Cannabidiol

Cannabidiol (CBD) is a chemical compound present in *Cannabis sativa* L. (*Cannabis spp.* or *Cannabis*); it can be isolated from either marijuana or hemp. In 2018, FDA approved Epidiolex as a Schedule V prescription medication for treatment of seizures caused by Lennox-Gastaut syndrome and Dravet syndrome. CBD derived from marijuana is classified as a Schedule I controlled substance, whereas hemp derivatives are legal federally and in most states. Hemp has $\leq 0.3\%$ (on a dry weight basis) concentrations of the psychoactive compound delta-9-tetrahydrocannabinol (THC). Prior to the approval of Epidiolex, CBD was classified as an Investigational New Drug; therefore, FDA explicitly states that CBD products cannot be defined as a dietary supplement.^a However, CBD is being widely marketed as a topical natural product in community pharmacies as creams, sprays, or roll-ons, as well as in smoke and vape shops.^b Additional regulations of products for oral ingestion are forthcoming from FDA.^c Although evidence to support seizure disorders is strong, data for use in other conditions such as anxiety, schizophrenia, pain, and spasticity are limited.^{d,e} Clinical trials are lacking for topical use in humans.

^a Corroon J, Kight R. Regulatory status of cannabidiol in the United States: A perspective. *Cannabis Cannabinoid Res.* 2018;3(1):190–194. doi: 10.1089/can.2018.0030.

^b Schiller M. CVS and Walgreens plan to carry CBD products: What's next for the rapidly growing market? *Cannabis Bus Times.* April 11, 2019. Available at: <https://www.cannabisbusinesstimes.com/article/cvs-walgreens-carry-cbd-products-whats-next-for-market/>. Accessed September 6, 2019.

^c U.S. Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, MD, on new steps to advance agency's continued evaluation of potential regulatory pathways for cannabis-containing and cannabis-derived products. April 2, 2019. Available at: <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-new-steps-advance-agencys-continued-evaluation>. Accessed

September 6, 2019.

^d Elliott J, DeJean D, Clifford T, et. al. Cannabis-based products for pediatric epilepsy. A systematic review. *Epilepsia*. 2019;60(1):6–19. doi: 10.1111/epi.14608.

^e White CM. A review of human studies assessing cannabidiol's (CBD) therapeutic actions and potential. *J Clin Pharmacol*. 2019;59(7):923–934. doi: 10.1002/jcph.

Ginkgo

Ginkgo biloba is a tree and the only living member of the family Ginkgoaceae.

Therapeutic Uses

Ginkgo has been used for Alzheimer's disease (AD), vascular dementia, attention-deficit/hyperactivity disorder (ADHD), tardive dyskinesia, intermittent claudication, tinnitus, acute mountain sickness, and age-related macular degeneration.

Physiologic Activity

The standardized *G. biloba* (EGb 761) concentrated (50:1) leaf extract contains ginkgolides (A, B, C, and M) and bilobalide. These constituents may be responsible for neuroprotective properties reported with the leaf extract. Ginkgolide B is a potent platelet-activating factor antagonist. The extract also contains bioflavonoids and flavone glycosides, such as quercetin, 3-methyl quercetin, and kaempferol. The flavonoid fractions may possess antioxidant and free radical scavenger effects.⁷⁰

Dosage and Product Considerations

Recommended dosages for dementias, intermittent claudication, and ADHD range between 120 and 240 mg daily of ginkgo leaf extract in 2–3 divided doses. EGb 761 is used in many clinical trials; formulations containing 24% ginkgo flavone glycosides and 6% terpenoids are available.⁷⁰

Safety Considerations

Studies have shown ginkgo to be generally well tolerated. Mild GI adverse effects, headache, dizziness, and allergic skin reactions have been reported.⁷¹ Ginkgo should be avoided during pregnancy and lactation because of the lack of safety information. Several potential drug interactions with ginkgo are listed in [Table 51–2](#).^{71,72}

Increased bleeding risk has been associated with use of ginkgo, although the evidence has been contradictory.^{68,73} A large retrospective analysis found the risk of bleeding increased about 40% with concurrent use of ginkgo and antithrombotic agents.⁷⁴ Patients taking antithrombotic agents should use ginkgo with caution.

Summary of Clinical Evidence

When combined with medications for treatment of cognitive impairment and dementia, ginkgo may provide modest benefit. A systematic review of 10 systematic reviews, the majority of which were high quality, evaluated ginkgo's effectiveness for treatment of mild cognitive impairment and dementia (both AD and vascular). Ginkgo combined with conventional medications resulted in improvement of cognition and daily activities. Daily dosages of 240 mg or higher reported the greatest benefit. Prevention of cognitive decline also was examined, but the study lacked consistent efficacy data to support benefit.⁷⁵ Evidence is lacking for prevention of cognitive decline in healthy individuals.

Melatonin

Therapeutic Uses

Melatonin, a hormone and potent antioxidant produced by the pineal gland, is synthesized from tryptophan via a serotonin pathway. Melatonin has FDA orphan drug status for sleep disorders in blind patients. The dietary supplement form of melatonin is used primarily for insomnia, prevention of “jet lag,” and sleep issues related to shift work.

Physiologic Activity

Melatonin regulates sleep and circadian rhythms; its release is induced by

darkness and suppressed by light, especially blue light emitted by phone and computer screens. Exogenous administration stimulates sleep regulation mechanisms. Melatonin usually does not cause “sleepiness,” although some morning drowsiness can occur as a side effect; rather, it may make attempts to sleep more successful. Melatonin has regulatory effects on sexual development and ovulation, and it may have effects on bone regulation.^{76,77}

Dosage and Product Considerations

For insomnia, 0.3–5 mg is taken orally 30–60 minutes prior to bedtime. For jet lag, the dosage is 2–5 mg taken the evening (between 5:00 and 10:00 pm) of arrival at the destination and at bedtime for the following 2–5 days. The dosage for occasional insomnia is unclear; supraphysiologic concentrations are produced by a 0.3 mg dose, and higher doses may not be more effective.⁷⁸

Most melatonin supplements are synthetically produced. Melatonin extracted from bovine pineal glands should be avoided because of the added risk of bacterial contamination and bovine spongiform encephalitis (mad cow disease). Some wine varieties contain small amounts of melatonin that are naturally produced during fermentation.

Safety Considerations

Rare adverse effects include nausea and vomiting, headache, irritability, dysthymia and worsening of depressive symptoms, and morning grogginess. A 2019 meta-analysis systematic review of melatonin’s adverse effects suggests that most can be ameliorated by dosing in concordance with circadian rhythms.⁷⁹ Long-term use should be under the supervision of a primary care provider.

Although melatonin is safe to use in younger children, use in adolescents is controversial because of possible hormonal effects on sexual development; any use in children in or around the age of puberty should be discussed first with a primary care provider. Pregnant and lactating women should not use melatonin.

Melatonin has variable effects on cancer treatments; patients should discuss melatonin with their oncologists before any use.⁸⁰

Summary of Clinical Evidence

Evidence of melatonin's effectiveness for occasional or primary insomnia in generally healthy people is variable, although a meta-analysis concluded that melatonin had small but clinically significant improvements in sleep quality.⁷⁸ Beneficial responses, including improved sleep and daytime behaviors, have been demonstrated more consistently in chronic sleep disorders, as well as in children and adults who have developmental disabilities, neurologic disorders, or autism.^{81,82} Depressed patients with sleep disorders may experience additional benefits for mood, although a systematic review of melatonin as a mood disorder treatment found that improvement was not significant, as measured by the standardized mean difference (SMD) of mood scales (SMD 0.37, 95% CI -0.05 to 0.37)).⁸³ Older patients (ages 55–80 years) may respond better to melatonin regardless of their endogenous levels, and prolonged-release formulations have improved sleep quality, daytime alertness, and psychomotor performance in this population.^{84,85} In patients treated with beta-blockers, 2.5 mg of melatonin for 3 weeks improved sleep time and efficiency.⁸⁶ Because of its mild adverse effect profile, melatonin may be an option on a trial basis for many individuals, albeit they should be counseled that the benefits may be small.

A 2014 meta-analysis concluded that melatonin used for insomnia caused by shift work may increase the duration of sleep slightly, but it does not improve sleep quality or symptoms such as sleepiness during the work shift.⁸⁷

Melatonin can decrease jet lag when five or more time zones are crossed. Its effects are greater for eastward travel than westward, and individual responses vary. The amount and timing of daylight exposure after arrival can decrease benefits.⁸⁸ Melatonin may not be as effective as zolpidem for sleep improvement or daytime tiredness associated with jet lag.⁸⁹

St. John's Wort

Hypericum perforatum, also known as St. John's wort, is a perennial with more than 400 species that grow wild throughout Europe, Asia, North America, and South America. The yellow flowers and the leaves contain the highest levels of medicinally useful compounds. St. John's wort (SJW) is classified in the Clusiaceae family but also may be listed under the Hypericaceae family.

Therapeutic Uses

SJW is used to treat depression, pain, anxiety, obsessive-compulsive disorder, menopause symptoms, and premenstrual syndrome.

Physiologic Activity

Although hypericin previously was considered to have antidepressant activity, evidence now indicates that hyperforin and its related compounds are primarily responsible. Other potential biologically active constituents include flavonoids and its derivatives, as well as procyanidins tannins, volatile oils, amino acids, phenylpropanes, and xanthones. SJW may modulate serotonin, dopamine, and norepinephrine. Additional data suggest that SJW also may activate GABA and glutamate receptors, and that it may potentially inhibit monoamine oxidase inhibitor.⁹⁰

Dosage and Product Considerations

The dosage of SJW for adults with mild to moderate depression is 900–1800 mg daily of a standardized extract of 0.3% hypericin or 2%–5% hyperforin. SJW should be taken in 3 divided doses with meals. Extracts commonly used in clinical studies include LI 160, ZE 117, WS 5570, STW3, and STW3-VI. The content of hypericin and hyperforin can vary in commercial preparations, and these products may not be interchangeable. As with prescription antidepressants, the therapeutic effects of SJW are not evident for several weeks. Depression should never be self-diagnosed or self-treated. Patients should seek appropriate medical care before using SJW.

Safety Considerations

An analysis of randomized trials found that rates of adverse effects in participants taking SJW were similar to those taking a placebo. In addition, the rates for SJW were lower compared with selective serotonin reuptake inhibitors (SSRIs).⁹¹ The most commonly reported adverse effects include nausea, fatigue, and skin reactions. Photosensitivity reactions have been reported, so patients should limit their exposure to sun and apply sunscreen before exposure.⁹² SJW should be avoided in patients with bipolar disorder and schizophrenia. As with SSRIs, SJW may cause sexual dysfunction. Abrupt discontinuation after chronic use may result in withdrawal symptoms similar

to those of conventional antidepressants. Limited evidence is available to assess the safety of SJW during pregnancy and lactation.

Interactions with SJW are well documented and clinically significant ([Table 51-2](#)). SJW is a potent inducer of CYP3A4, resulting in significantly lower concentrations of drugs metabolized through this pathway.⁹² Oral contraceptives therefore may be less effective, so patients should use a second form of birth control. The extent of induction may correlate with hyperforin dose and varies among products. SJW also may induce P-glycoprotein transport proteins, resulting in lower serum concentrations of drugs. Additional evidence suggests induction of other CYP substrates, such as CYP2C19. If taken with other serotonergic agents, SJW may increase the risk of developing serotonin syndrome.⁹²

Summary of Clinical Evidence

SJW may be as effective as many antidepressants for mild to moderate depression, with fewer adverse effects. A Cochrane review that evaluated *Hypericum* extracts for major depression included 18 placebo-controlled trials and 17 studies with an active control. SJW had a significant benefit for mild to moderate depression compared with placebo; its efficacy was similar to that of standard antidepressants, such as SSRIs or tricyclic antidepressants. The rates for adverse effects and trial discontinuation also were lower with SJW than with older antidepressants, indicating that *Hypericum* extract may be more tolerable. In addition, the results vary depending on the country of origin, with German-speaking countries showing better outcomes. Conclusions about its efficacy in treating severe depression cannot be made.⁹³ A subsequent systematic review that included 35 studies found similar results regarding efficacy. Compared with users of antidepressants, SJW users were less likely to experience adverse effects; SJW and placebo users experienced comparable effects. The majority of studies included information on adverse effects from SJW use, but few were specifically designed to assess this outcome.⁹⁴ Because of its drug interactions and the potential seriousness of depression, SJW is not an appropriate choice for many patients.

Valerian

Native to Europe and Asia, valerian grows in most parts of the world. More than 200 plant species belong to the genus *Valeriana*. The most common plant

used from the Valerianaceae family for medicinal purposes is *Valeriana officinalis*.

Therapeutic Uses

Valerian is used for alleviating insomnia and anxiety.

Physiologic Activity

The CNS activity of valerian may be related to the valepotriates and sesquiterpene constituents of the volatile oils. Other active components include alkaloids, furofuran ligans, and free amino acids, including GABA. Valeric acid and other components likely interact with GABA receptors in the brain, with the valproates and valeric acid producing sedation.⁹⁵

Dosage and Product Considerations

Most clinical trials for insomnia use valerian root extract 400–900 mg, administered 30–120 minutes before bedtime. Teas can be prepared from dried roots, although they often have an unpleasant taste and smell. Combination products containing hops or lemon balm are commonly marketed.

A Word About Kava

Kava is derived from the rhizome and roots of *Piper methysticum* and is used widely by Pacific Islanders as a social and ceremonial tranquilizing beverage; it has been used to treat mild anxiety and sleep disturbances.^a In 2002, the Center for Food Safety and Nutrition issued a warning advising consumers and professionals of the risk of severe liver injury associated with kava-containing supplements. Germany, Switzerland, Canada, Australia, and France have restricted the sale of kava products in response to case reports of liver failure associated with use.^b Several factors related to the origin of liver injury are in question. These include aqueous versus acetone or ethanol extracts, continuous high doses, inappropriate raw products, and potential contaminants. No updates to the consumer advisory have been made.^c A systematic review and meta-analysis including randomized clinical trials examined kava's efficacy in

light of potential toxicity. Data from five trials found kava slightly more efficacious for anxiety than placebo with RR of 1.5 (95% CI 1.2–2.01), with most benefit noted in younger populations and females. Adverse effects were similar to placebo; however, no trial continued beyond 8 weeks.^d Until further data that identify the cause of liver injuries are available, patients should avoid taking kava.

^a Sarris J, LaPorte E, Schweitzer I. Kava: a comprehensive review of efficacy, safety, and psychopharmacology. *Aust N Z J Psychiatry*. 2011;45(1):27–35. doi: 10.3109/00048674.2010.522554.

^b Centers for Disease Control and Prevention. Hepatic toxicity possibly associated with kava-containing products—United States, Germany, and Switzerland, 1999–2002. *MMWR Morb Mortal Wkly Rep*. 2002;51(47):1065–1067. Available at: <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5147a1.htm>. Accessed March 12, 2019.

^c Teschke R, Lebot V. Proposal for a kava quality standardization code. *Food Chem Toxicol*. 2011;49(10):2503–2516. doi: 10.1016/j.fct.2011.06.075.

^d Smith K, Leiras C. The effectiveness and safety of Kava Kava for treating anxiety symptoms: a systematic review and analysis of randomized clinical trials. *Complement Ther Clin Pract*. 2018 Nov;33:107–117. doi: 10.1016/j.ctcp.2018.09.003. Epub 2018 Sep 15.

Safety Considerations

Valerian is generally well tolerated with headache, excitability, and paradoxical insomnia occurring infrequently. Benzodiazepine-like withdrawal symptoms have been reported after discontinuation of valerian, and residual daytime sedation has been associated with higher dosages (900 mg). *Valeriana officinalis* preparations are safe despite the known in vitro cytotoxic activity of valepotriates, which generally are not found in products. Chronic administration has been linked to hepatotoxicity, although the reports included combination products and the role of valerian was unclear. Valerian can potentiate the effects of other CNS depressants, so they should not be taken concomitantly. Pregnant women should avoid the use of valerian

because of potential induction of uterine contractions.⁷¹

Summary of Clinical Evidence

A meta-analysis of 18 randomized, placebo-controlled trials evaluated the effect of valerian on insomnia. Eight trials were of high quality. Subjective improvements were reported for insomnia, although the overall effectiveness of valerian could not be assessed.⁹⁶ A study of older adults found *V. officinalis* to be inferior to temazepam and diphenhydramine.⁹⁷ Limited evidence exists to suggest valerian is efficacious.

Gastrointestinal System

Ginger

Ginger (*Zingiber officinale*) is a perennial from the Zingiberaceae family whose rhizomes and roots are used medicinally.

Therapeutic Uses

The primary use of ginger has been to relieve nausea and vomiting associated with pregnancy, motion sickness, chemotherapy, and surgery. Ginger also has been used for indigestion, colic, and arthritis.

Physiologic Activity

Ginger rhizomes possess a volatile oil that contains sesquiterpene hydrocarbons, including zingiberene and alpha curcumene, with lesser amounts of farnesene, beta sesquiphellandrene, and beta bisabolene. Ginger also contains an oleoresin with nonvolatile pungent components, including gingerol, shogaols, and zingerone. Galanolactone, a diterpenoid isolated from ginger, and 6-shogaol have anti-5-hydroxytryptamine activity in the GI tract, which possibly contributes to ginger's antiemetic activity. Ginger does not affect GI motility or increase gastric emptying. The 6-shogaol and 6-gingerol components inhibit cyclooxygenase (COX) and lipoxygenase pathways, resulting in anti-inflammatory actions and potential inhibition of platelet thromboxane.⁹⁸

Dosage and Product Considerations

Dried ginger 250 mg taken 4 times daily has been used for nausea and vomiting in pregnancy. For motion sickness, a typical dosage is 500 mg of dried powdered ginger root taken 30 minutes before travel, followed by 1–2 additional 500 mg capsules as needed every 4 hours. Daily dosages greater than 4 g should be avoided.

Safety Considerations

Mild heartburn and belching have been reported with ginger. Ginger may increase the risk of hypoglycemia.⁷¹ Ginger also may alter platelet function, although findings are mixed; ginger should be used with caution by individuals taking antithrombotic agents.^{68,72}

Randomized controlled trials have not identified significant adverse effects on pregnancy outcomes between ginger and placebo or pyridoxine.^{99,100} A Norwegian population-based cohort study found no increase in malformations, fetal death, premature birth, low birth weight, or Apgar scores below 7. About 45% of the cohort ingested ginger during the first trimester, although timing of exposure and dosing was lacking. A small, but significant, increase in vaginal bleeding was noted after week 17 (7.8% vs. 5.8%) compared with controls.¹⁰¹ In a review of clinical evidence that focused on safety, investigators concluded that ginger appeared to be safe and effective for short-term use in nausea and vomiting in pregnancy, but stressed that patients should use only high-quality products and should be monitored by a health care provider. The potential for bleeding also should be considered.¹⁰²

Summary of Clinical Evidence

Results for ginger's efficacy in the management of postoperative and chemotherapy-induced nausea and vomiting have been mixed. A meta-analysis of 10 randomized controlled trials involved more than 900 subjects who used a visual analogue scale (VAS) to rate the effectiveness of ginger in the management of postoperative nausea and vomiting. Researchers concluded that ginger was effective in decreasing severity episodes. The incidence was not significantly reduced, possibly because of under dosing.¹⁰³ A systematic review of five randomized, controlled trials, encompassing more than 800 subjects, compared ginger with metoclopramide or placebo for

treatment of chemotherapy-induced nausea and vomiting. Ginger did not control the severity or incidence of acute nausea.¹⁰⁴ Another meta-analysis of 10 studies demonstrated benefit from use of ginger in chemotherapy-induced nausea and vomiting, specifically within an acute onset subgroup.¹⁰⁵

A systematic review and meta-analysis of pregnancy-induced nausea and vomiting evaluated 12 randomized controlled clinical trials. Studies varied in size, dosage of ginger, duration of treatment, and comparative treatments (placebo, pyridoxine, dimenhydrinate, or metoclopramide). Compared with the placebo group, use of ginger in early pregnancy improved symptoms of nausea but not the overall number of vomiting episodes. Comparison of ginger with pyridoxine in two of the studies showed no differences. Daily dosages of less than 1500 mg were most effective.¹⁰⁰ A Cochrane review concluded that ginger may have a role in early pregnancy for nausea and vomiting.¹⁰⁶ The American College of Obstetricians and Gynecologists (ACOG) practice guidelines includes ginger as an option with beneficial effects rated as level evidence B, suggesting limited or inconsistent evidence, in treating nausea and vomiting in pregnancy.¹⁰⁷ Because the effectiveness of ginger for hyperemesis gravidarum is limited, ginger should not be recommended for this condition.

Milk Thistle

Silybum marianum, or milk thistle, is a member of the Asteraceae/ Compositae family.

Therapeutic Uses

Milk thistle has been used to treat liver disease, including hepatitis and cirrhosis, and diabetes. In Europe, it is used to treat poisoning by the mushroom *Amanita phalloides* (death cap). Milk thistle has been used as a liver protective agent for exposure to alcohol, acetaminophen, and carbon tetrachloride.

Physiologic Activity

Milk thistle's seeds and fruit contain several compounds, generally referred to as silymarin. Major flavonolignans include silybin, isosilybin (A & B), silydianin, and silychristin.¹⁰⁸ These biologically active compounds have antioxidant,

antifibrotic, immunostimulating, and anti-inflammatory activity, in addition to other beneficial effects such as regulation of cell permeability and inhibition of mitochondrial injury. Stimulation of polymerase I, resulting in increased ribosomal protein synthesis, stimulates liver regeneration and the formation of new hepatocytes. The antioxidant properties of silymarin may be the primary beneficial effect.

Dosage and Product Considerations

The average dosage is silymarin 140 mg taken 3 times daily or silybin (silibinin) 240 mg twice daily. Milk thistle preparations contain varying amounts of a concentrated seed extract, standardized to flavonolignans 70%–80% calculated as silymarin; approximately 70% is silybin. Multiple products of silymarin and silybin have been used in clinical studies, but they may not be available in the United States, even with identical standardization. Liver disease resulting from alcohol, acetaminophen, and other drugs or chemicals is potentially fatal, and patients should be cautioned against self-treatment with milk thistle.

Safety Considerations

Milk thistle is generally well tolerated. Pregnant women and patients with an allergy to ragweed and other members of the Asteraceae/Compositae family should avoid the use of milk thistle. The product may stimulate lactation, although evidence is limited.¹⁰⁹ Most, but not all, studies indicate that milk thistle does not inhibit several CYP isoenzymes and P-glycoprotein, thereby reducing the likelihood of drug interactions.⁷²

Summary of Clinical Evidence

Evidence to support the use of milk thistle in liver disease is limited. A Cochrane review of 18 randomized controlled studies investigated its effect on liver disease caused by alcohol or hepatitis B or C viral infection. Reductions in mortality or complications of liver disease or changes in liver histology were not identified. Liver-related mortality was significantly reduced with inclusion of all trials but not in the five high-quality trials.¹¹⁰ A meta-analysis of five randomized controlled trials that included participants with chronic hepatitis C virus found no significant benefit in reduction of levels of serum alanine aminotransferase or hepatitis C virus RNA, or changes in quality of life.¹¹¹ Milk thistle has not been compared with the new treatments for hepatitis C and

should never be used in place of antiviral therapy.

A systematic review of milk thistle administration in patients with type 2 diabetes found potential benefit in glycemic control, with a reduction of fasting glucose numbers and hemoglobin A1C. The five studies were small, totaling 270 subjects, varied in duration of treatment and amount of silymarin taken, and lacked long-term clinical outcomes to generally support use for diabetes.¹¹²

Peppermint

Mentha piperita, or peppermint, is a member of the mint family Lamiaceae. It has been cultivated for its fragrant volatile oil, which is extracted primarily from leaves of the plant.

Therapeutic Uses

Both peppermint leaf and oil have been used for treatment of irritable bowel syndrome (IBS), nonulcerative dyspepsia, colonic spasm, and tension headache.

Physiologic Activity

The activity of peppermint may be a result of its 0.5%–4% essential oil. The oil or leaf preparations should be standardized to contain not less than 44% menthol. Menthol stereoisomers also are present, including 3% *d*-neomenthol and menthone, menthofuran, eucalyptol, and limonene. The mechanism of action of peppermint involves direct relaxation of GI smooth muscle.

Dosage and Product Considerations

The usual dosage of peppermint oil enteric-coated capsules for IBS is 0.2–0.4 mL (187–374 mg) taken 3 times daily 15–30 minutes before meals. Enteric-coated preparations reduce risk of heartburn. Clinical trials have studied 8–16 mL of peppermint oil solution as an antispasmodic.¹¹³

Safety Considerations

Heartburn may be attributed to relaxation of the lower esophageal sphincter.

Patients who have severe preexisting gastroesophageal conditions should avoid use of peppermint oil. Peppermint leaf tea or topical products should be used with caution in infants and small children because of possible laryngeal and bronchial spasms from volatilized menthol. The oil also may irritate mucous membranes; theoretically enteric-coated capsules will minimize this effect. Antacids or other medications that increase stomach pH may affect dissolution of enteric-coated capsules. Data suggest that peppermint may decrease activity of CYP3A4 for drugs such as felodipine.⁷² Further, the ingestion of peppermint may decrease absorption of iron.⁷¹

Summary of Clinical Evidence

A systematic review and meta-analysis of nine studies with enteric-coated peppermint oil capsule demonstrated short-term safety and efficacy in participants with IBS. Significant differences were found in global improvement of IBS symptoms (392 participants) and abdominal pain (357 participants) compared with placebo.¹¹⁴ A higher rate of adverse events were reported in the peppermint oil groups, with heartburn as the most common symptom. A subsequent pooled meta-analysis of 12 studies found additional safety and efficacy evidence to support peppermint oil administration in IBS for pain (556 participants) and global improvement of symptoms (507 participants). Compared with placebo, the number needed to treat to detect improvement in global symptoms was 3, and 4 were needed for abdominal pain. No significant differences were noted in adverse effects.¹¹⁵

Endocrine System

Alpha-Lipoic Acid

Therapeutic Uses

Alpha-lipoic acid, or thioctic acid, is an endogenous antioxidant promoted for patients with diabetes. For diabetic peripheral neuropathy, both intravenous and oral dosage forms have been studied.

Physiologic Activity

Alpha-lipoic acid, synthesized from linoleic acid, is a cofactor for glucose

metabolism enzymes. Small amounts of the cofactor exist in plant and animal sources; the greatest amounts are attached to lysine in spinach and broccoli.¹¹⁶ Alpha-lipoic acid has hydrophilic and lipophilic properties. These properties allow it to serve as an antioxidant within both lipid membranes and aqueous environments, in constant regenerative balance with its reduced form, dihydrolipoic acid. Alpha-lipoic acid acts on glucose transporters and stimulates glucose uptake by various mechanisms, including effects on GLUT-1 and GLUT-4 receptors. In addition to improved nerve conduction and blood flow, human studies have shown improvement in insulin sensitivity and oral glucose tolerance tests.^{116,117}

Dosage and Product Considerations

With an oral bioavailability of 30%, 600 mg of alpha-lipoic acid taken 3 times daily is comparable to the 600 mg intravenous dosage used in many European trials for diabetic neuropathy.^{116,117} However, one study found patients who improved while taking 1800 mg a day orally were able to maintain benefits when the dosage was lowered to 600 mg once daily.¹¹⁸ Food decreases absorption, so alpha-lipoic acid should be taken on an empty stomach.¹¹⁹ It must not be taken within 2–3 hours of taking antacids or other mineral-containing supplements because of their chelating activity.¹¹⁹

Safety Considerations

Adverse effects are generally mild and include headache, nausea, diarrhea, and rash. Patients who wish to add alpha-lipoic acid to antidiabetic therapy should discuss its use with their health care provider. More frequent monitoring of glucose concentrations is advised during the initial weeks of therapy, because additive hypoglycemic effects may occur. Patients with thyroid conditions should avoid alpha-lipoic acid, because it can inhibit conversion of thyroxine to triiodothyronine and may displace thyroxine from serum-binding protein.

Summary of Clinical Evidence

Although not all trials have demonstrated improvements in neuropathic symptoms in patients with diabetes who take oral alpha-lipoic acid, three meta-analyses concluded that intravenous and oral supplementation is beneficial, with improvement in total symptom scores, neuropathy impairment scores, and short-term symptoms of pain and paresthesia.^{120–122} In

a rigorous 4-year study of 460 patients, alpha-lipoic acid was demonstrated to be more useful in preventing progression of neuropathy rather than being used as an acute treatment.¹²³ A study comparing oral alpha-lipoic acid with carbamazepine and pregabalin noted that the pain severity score on a VAS was significantly improved from baseline for alpha-lipoic acid and pregabalin.¹²⁴ Alpha-lipoic acid may be considered a treatment option for diabetic neuropathy.

In several neuropathy trials, reductions in glucose and hemoglobin A1C were not significant.^{120–122} Small trials over the last decade have documented clinically significant lowering of fasting blood glucose, insulin and hemoglobin A1C, primarily when alpha-lipoic acid was added to standard antidiabetic medications. A meta-analysis of these trials reported SMDs of -0.84 (95% CI -1.39 to -0.28), -0.50 (95% CI -0.88 to -0.12), and -1.17 (95% CI -2.12 to -0.20), respectively, which could be clinically significant for some patients.¹²⁵

Although a strong recommendation for glucose control cannot yet be made, alpha-lipoic acid's safety profile supports use in individual patients.

Cinnamon (Cinnamomum cassia or C. aromaticum)

Therapeutic Uses

Cinnamon, specifically *Cinnamomum cassia*, the type most commonly found in grocery spice aisles, is used to help lower blood glucose.

Physiologic Activity

Both *Cinnamomum cassia* and true cinnamon (Ceylon cinnamon; *C. verum* also known as *C. zeylanicum*) have components that affect glucose levels with differing mechanisms of action and have had similar results in preclinical studies.^{126,127} Cinnamtannin B1, a proanthocyanidin, triggers autophosphorylation of insulin receptors to increase insulin sensitivity.¹²⁷ Cinnamaldehyde increases cellular glucose uptake by stimulating glucose transporter-1 (GLUT-1) and GLUT-4 receptors.¹²⁷ Water-soluble extracts of both *C. cassia* and *C. verum* activate PPAR-alpha and PPAR-gamma in a manner similar to that of pioglitazone, and they display inhibition of amylase and sucrose.¹²⁷ Cinnamon inhibits inactivation of insulin receptors by tyrosine

phosphatase; anti-inflammatory actions occur through changes in multiple cytokines involved in the inflammatory process.¹²⁶ Whole cinnamon seems to delay gastric emptying, which could reduce postprandial glucose spikes.

Dosage and Product Considerations

Aqueous extracts may be most effective; the dosage is 0.5–1 daily of *C. cassia* extract. The dose of ground cinnamon (*C. cassia*) is 2–6 g, given in divided doses either in capsules or sprinkled in food. A half-teaspoonful is approximately 1 g.¹²⁸

Safety Considerations

Patients should not confuse cinnamon supplements with cinnamon oil; hypersensitivity reactions to the oil can occur, as well as pediatric poisoning from ingestion.¹²⁸ Attempted ingestion of dry cinnamon powder, generally by adolescents undergoing a challenge, has led to severe adverse effects.¹²⁹ Other than allergic reactions, no adverse events have been reported in trials. One case report exists of probable medication-induced hepatitis; cinnamon is known to contain coumarins (much greater amounts in *C. cassia* than in *C. verum*) that can be hepatotoxic.¹³⁰ Potentiation of hypoglycemic reactions in patients on hypoglycemic medications is theoretically possible, but not noted in clinical trials with patients on standard treatments.

Summary of Clinical Evidence

C. verum has not received the same clinical evaluations as *C. cassia*. One human clinical trial of *C. verum* demonstrated no effect on glucose or insulin levels, whereas a human laboratory study did note reductions in the postprandial glycemia AUC.^{131,132}

Clinical trials of *C. cassia* have had contradictory results for glucose control. In general, negative trials used 1–1.5 g daily, whereas studies with positive outcomes used 3–6 g daily or equivalent aqueous extract.^{133,134} A well-designed trial of 2 g daily of ground cinnamon added to standard antidiabetic medications reduced mean hemoglobin A1C from 8.22% to 7.86% after 12 weeks, a significantly greater effect than seen with placebo.¹³⁵ A 3-month trial of low doses of cinnamon aqueous extract (120 and 360 mg daily) added to sulfonylurea therapy showed significantly reduced fasting blood glucose and

hemoglobin A1C levels compared with placebo.¹³⁶ Data from the most recent meta-analysis showed that fasting blood glucose levels were significantly reduced compared with placebo, -19.26 mg/dL (95% CI -28.08 to -10.45 , $P = 0.0001$); however, hemoglobin A1C levels were not, -0.24 (95% CI -0.48 to -0.01 , $P = 0.0001$).¹³⁷ The effect size of cinnamon on fasting plasma glucose or hemoglobin A1C can be expected to be small.¹³⁴ More study is needed, but the favorable safety profile means that cinnamon is an adjunctive option in some patients, especially those attempting to control blood glucose primarily through lifestyle changes.

A Word About Chromium

Chromium is a popular ingredient in supplements for patients with diabetes. Absorption of elemental chromium depends on an individual's chromium status and the salt form; chromium from brewer's yeast and the picolinate salt are the most well absorbed.^a The Cr^{+3} ion is a component of the glucose tolerance factor protein. Chromium also is involved in multiple processes in the body that involve carbohydrate and lipid metabolism; however, the exact mechanisms remain unclear. Theories include insulin signal amplification, direct activation of insulin receptors, and influence on estrogen receptors. Chromium does have a mild adverse event profile; in clinical trials, rates were similar to placebo and reports included headache, nausea, loose stools and constipation, and flatulence.^b

Does chromium improve glucose control in patients with diabetes? The answer to that question remains controversial. The two most recent meta-analyses, published in the same year, came to opposing conclusions. The first found that in 22 trials reporting fasting plasma glucose, the mean decrease was 20.34 mg/dL (95% CI -35.46 to 5.4) and the decrease in hemoglobin A1C was -0.58 (95% CI -0.93 to -0.23).^b Lipids were less affected, with only mean triglyceride reduction by chromium picolinate found to be significant at -26.57 mg/dL (95% CI -43.4 to -9.74). The second meta-analysis used a different statistical approach and examined effect size on fasting plasma glucose in 18 trials.^c The researcher reported a nonsignificant weighted average effect size at 0.02 (95% CI -0.12 to 0.16 , $P = 0.787$). More research is warranted to determine a realistic impact of

chromium in patients with diabetes as well as an optimum dosage. Until then, chromium should be used cautiously and dosages limited to ~200 mcg daily.

^a Lewicki S, Zdanowski R, Kryzyz'owski M, et al. The role of chromium III in the organism and its possible use in diabetes and obesity treatment. *Ann Agricultural Environ Med*. 2014;21(2):331–335. doi: 10.5604/1232-1966.1108599.

^b Suksomboon N, Poolsup N, Yuwanakorn A. Systematic review and meta-analysis of the efficacy and safety of chromium supplementation in diabetes. *J Clin Pharm Therap*. 2014;39:292–306. doi: 10.1111/jcpt.12147.

^c Bailey CH. Improved meta-analytic methods show no effect on chromium supplements on fasting glucose. *Biol Trace Elem Res*. 2014;157:1–8. doi: 10.1007/s12011-013-9863-9.

A Word About Bitter Melon

The fruit of *Momordica charantia* historically has been used both as a food and a medicine for diabetes. As a food, it is often prepared with sugar to counteract the bitterness. Multiple mechanisms are involved in its actions on blood glucose, including increased cellular glucose uptake, decreased gluconeogenesis in the liver, and increased insulin secretion. A 2019 meta-analysis that included 10 trials found that bitter melon was able to significantly reduce fasting plasma glucose, postprandial glucose, and hemoglobin A1c by 12.96 mg/dL, 25.74 mg/dL, and 0.26%, respectively.^a An additional 2018 study demonstrated similar effects on glucose outcomes as well as changes in lipid measurements, some of which reached significance: decreased TC, LDL cholesterol, and LDL/HDL ratio, and increased HDL cholesterol.^b Bitter melon is well tolerated with primarily GI side effects, such as nausea, heartburn, and diarrhea.

^a Peter EL, Kasali FM, Deyno S, et al. *Momordica charantia* L. lowers elevated glycaemia in type 2 diabetes mellitus patients: systematic review and meta-analysis. *J Ethnopharmacol*. 2019;321:311–324. doi: 10.1016/

j.jep.2018.10.033.

^b Kumari S, Dash I, Behera KK. Therapeutic effect of *Momordica charantia* on blood glucose, lipid profile and oxidative stress in type 2 diabetes mellitus patients: a randomized controlled trial. *J Clin Diag Res*. 2018;12(9):BC21– BC25. doi: 10.7860/JCDR/201/36354.12036.

Immune Modulators

Echinacea

Echinacea species used in self-care include *E. purpurea*, *E. angustifolia*, and *E. pallida*. Roots, leaves, and flowers are used medicinally. Depending on the species, the above-ground parts may have more activity.

Therapeutic Uses

Echinacea is used to prevent and treat colds and other respiratory infections.

Physiologic Activity

Echinacea has many components that target the nonspecific cellular immune system, including alkylamides, chicoric acid, flavonoids, glycoproteins, and polysaccharides. Multiple mechanisms of action are involved in the effects, including increased cytokine secretion, lymphocyte activity, and phagocytosis. Direct inactivation of viruses, bacteria, and fungi has been observed.¹³⁸ Anti-inflammatory activities and decreases in mucin production are likely to be more directly responsible for decreased symptoms of upper respiratory infections.¹³⁸ Some of the immunostimulatory activity is caused by lipopolysaccharides and xanthienopyran produced by endophytic bacteria that live within the plant.¹³⁹ The activity is not present in extracts from plants grown from sterilized seed. Bacterial load may vary between plants, and the extraction processes may affect the content of these components, which may explain the varied results in clinical trials.

Dosage and Product Considerations

Products labeled “echinacea” may be chemically different plants or plant parts, making comparisons difficult. The optimum standardization and dose for echinacea are unknown. Standardized concentrates, such as Echinaforce, generally perform better in trials. Echinacea is available in single- and multiple-ingredient formulations such as teas, extracts, juices, throat sprays, capsules, and tablets; each formulation has its own dosing regimen. Many products available in the United States are less concentrated or are labeled for use at doses much lower than those used in clinical trials and may be ineffective if used as directed. For greatest efficacy, all formulations must be taken at the first sign of illness.

Safety Considerations

Allergic reactions may occur with use of echinacea. Patients with a history of asthma or atopy should avoid echinacea; a severe allergy to the *Asteraceae/Compositae* family, which includes ragweed and chrysanthemums, is also a contraindication. Adverse effects include mild GI discomfort and headache. More serious reactions are possible: after taking an echinacea root product for 5 days while ill with a flu-like syndrome, one patient developed acute cholestatic hepatitis, which resolved quickly after product discontinuation.¹⁴⁰ Echinacea should not be used by patients with severe systemic illnesses such as HIV infection or AIDS, multiple sclerosis, tuberculosis, and autoimmune disorders, and by patients taking immunosuppressants; this concern is based on case reports and theory.¹⁴¹ Echinacea exhibits some effects on P-glycoprotein transport and several intestinal and hepatic CYP450 systems; however, these effects are not likely to be significant except for drugs with a narrow therapeutic range.¹⁴² A systematic review of echinacea use during pregnancy found no differences in rates of major malformations.¹⁴³

Summary of Clinical Evidence

Individual trials for either treatment or prevention of colds or upper respiratory infections have had widely variable results, making conclusions difficult. This may be a result of disparate doses, concentrations, plant species and parts, or extraction methods used for the study products.

For prevention, a 2015 meta-analysis that examined echinacea's impact on recurrent infection risk when used continuously for 2–4 months or in repetitive 10-day treatments over 4 months concluded that treatment resulted in a relative risk (RR) of recurrent infection of 0.649 compared with placebo ($P < 0.0001$).¹⁴⁴ A 2019 meta-analysis determined a risk ratio of 0.78 (95% CI 0.68–0.88) for prevention, but investigators cautioned that the significant heterogeneity in trial results limited the usefulness of their conclusion.¹⁴⁵

For treatment, the evidence also is mixed. A 2007 meta-analysis of 14 randomized placebo-controlled studies found a significant reduction in duration of 1.4 days.¹⁴⁶ A 2019 meta-analysis of seven studies determined a nonsignificant mean difference in illness duration of –0.45 (95% CI –1.85 to 0.84), compared with placebo.¹⁴⁵ Further study will have to determine the true effect size of treatment, but current treatment trial data do indicate that best results occur when echinacea is administered at the first sign of symptoms.

Echinacea's immunostimulatory effects were tested in a well-designed pilot study in adults with respiratory disease that compared rates of influenza- and parainfluenza-like symptoms and respiratory complications. Groups were given prophylactic doses of flu vaccine, a hydroalcoholic root extract of *E. angustifolia*, or both. Rates of symptoms were decreased for echinacea-only and echinacea+vaccine groups compared with the vaccine-alone group.¹⁴⁷ Parainfluenza-like symptoms occurred in five patients in the vaccine-only group and in only one patient in each of the echinacea-only and echinacea+vaccine groups.

Elderberry

Therapeutic Uses

Juice or extracts of the *Sambucus nigra* berry are used primarily for prevention or treatment of influenza and other upper respiratory illnesses.

Physiologic Activity

Elderberries contain many vitamins (C, B2, B6, folic acid, beta-carotene, and others) and multiple flavonoids, anthocyanins, and polysaccharides. The activities of elderberry include inhibition of virus replication, increased production of anti-inflammatory and inflammatory cytokines, strong

antioxidant capacity, increased number of viral antibodies, and inhibition of hemagglutination of the influenza virus, which prevents viral entry into cells.¹⁴⁸ Extracts have inhibited growth of gram-positive and gram-negative bacteria.¹⁴⁹

Dosage and Product Considerations

Clinical trials have used at least four elderberry dosage forms including a spray-dried juice (400 mg TID, 10% anthocyanins), a syrup standardized to flavonoid content (Sambucol), encapsulated extracts, and an infusion prepared daily from dried elderberries.^{150–153} The optimum standardization and dosage form have not been determined.

Safety Considerations

Commercially available elderberry extracts are well tolerated, with few adverse effects reported.^{151,152} Insufficiently cooked or unripe berries, stems, or leaves contain cyanogenic glycosides, which are metabolized to cyanide in the GI tract; reports exist of not only nausea and vomiting but also dizziness, weakness, and stupor with ingestion of home-prepared juices and extracts.¹⁵³ (See [Table 51–2](#) for possible drug interactions.)

Summary of Clinical Evidence

The first study of elderberry extract (Sambucol) utilized 30 mL (15 mL for children) daily for 3 days in patients reporting flu symptoms during an influenza B outbreak. Fever duration was 4 days versus 6 days in the treatment and placebo groups, respectively. After 3 days, “complete cure” was noted in 46.7% of elderberry-treated patients and 16.7% of the placebo group.¹⁵⁰ The second study ($N = 60$), conducted during an influenza A epidemic, noted that elderberry-treated patients reached scores closer to “pronounced improvement” (10 on a 0–10 VAS scale) more quickly (3–4 days) than did placebo-treated patients (7–8 days).¹⁵⁴ Elderberry-treated patients also used fewer rescue medications.

A combination elderberry and echinacea hot drink product was tested against oseltamivir in a randomized, double-dummy noninferiority trial of 473 patients with clinically diagnosed influenza.¹⁵⁵ “Recovery, (symptom alleviation) was similar at 5 and 10 days. 50.2% versus 48.8%, and 90.1% versus 84.8% in the hot

drink and oseltamivir groups, respectively. A subanalysis of patients with laboratory-confirmed influenza noted noninferiority at days 5 and 10, and the hot drink group experienced significantly greater recovery at day 10 than the oseltamivir group, 95% versus 76.2%, respectively. Complication rates were 2.5% and 6.5% in the hot drink and oseltamivir groups, respectively.

In a double-blind, placebo-controlled trial, elderberry extract was investigated for effectiveness in prevention and treatment of cold symptoms in air travelers.¹⁵³ Participants ($N = 312$) took a 300 mg capsule twice daily for 2–10 days prior to traveling, then thrice daily while traveling, and for 4 days after arriving overseas. Cold occurrence rates did not differ between the groups: 17 taking placebo and 12 taking elderberry. Average cold duration was 4.75 days and 6.88 days in the elderberry and placebo groups, respectively ($P = 0.05$). Symptom severity scores were 21 and 34 in the elderberry and placebo groups, respectively ($P = 0.02$).

More research is needed before a population recommendation can be made, but in light of the mild adverse effect profile, elderberry extracts may be an appropriate option for individual patients.

Probiotics

See [Chapter 20](#) for discussion of the immune modulation effects of probiotics.

Physical and Mental Performance Enhancers

Eleuthero (Siberian Ginseng)

Eleutherococcus senticosus from the Araliaceae family is often referred to as *Acanthopanax senticosus* or Siberian ginseng. The plant is not a genus of *Panax*, as are Asian and American ginseng species. *Eleutherococcus* is found in eastern Siberia, northeastern China, Korea, and Hokkaido Island in Japan.

Therapeutic Uses

Eleuthero's traditional use is as an adaptogen for improvement of athletic performance, chronic stress, upper respiratory conditions, and immune deficiency. Other uses include treatment of herpes simplex type 2 infections,

blood pressure, prevention of atherosclerosis, and diabetes mellitus.

Physiologic Activity

The active compounds of eleuthero, derived primarily from the root and leaf, are referred to as eleutherosides (subtypes A to M). Flavonoids, hydroxycinnamates, and other constituents such as sesamin, B-sitosterol, hederasaponin B, and isofraxidin also may have biological activity. Animal studies and in vitro analysis suggest these compounds have antiplatelet, immunostimulant, and antioxidant properties.¹⁵⁶

Dosage and Product Considerations

Commercial products often are standardized to eleutheroside B and/or E content at a dosage of 300–400 mg daily. A 33% ethanolic extract 10 mL taken 3 times daily also has been used. After 2 months of daily use, patients should discontinue the product for a minimum of 2 weeks.¹⁵⁶ Eleuthero may be found as an ingredient in energy drinks because of its caffeine-like effects.

Safety Considerations

Both drowsiness and stimulant effects similar to those of caffeine, have been reported with eleuthero. Because of its variable effects on blood pressure, eleuthero should be avoided in patients with hypertension. Theoretically, patients with diabetes mellitus should be monitored for hypoglycemia.¹⁵⁶ Safety data are lacking for use during pregnancy and lactation. In patients taking digoxin, eleuthero may interfere with digoxin assays because of the structural similarities of their glycosides.⁷²

Summary of Clinical Evidence

Well-designed, randomized clinical trials documenting the safety and efficacy of eleuthero are lacking. Most evidence exists in combination with other herbals for treatment of cough and cold. Double-blind, placebo-controlled studies have evaluated eleuthero in fixed combination with *Andrographis paniculata* for upper respiratory tract infections.¹⁵⁷ Improvements have been demonstrated on most symptoms; cough improved in the study only with the use of a combination product including *Echinacea purpurea*.^{156–158}

In a small 6-month study, *Eleutherococcus* extract taken once daily demonstrated a beneficial effect on frequency, severity, and duration of herpes simplex type 2 infections.¹⁵⁹ A study of 144 participants were assigned *E. senticosus* root extract 120 mg taken daily, professional stress management training, or a combination of both. Participants suffered from chronic stress and fatigue that resulted in impaired work capacity. All treatment groups improved similarly from baseline at weeks 2 and 8 in most parameters related to performance and stress; mental fatigue and alertness were significantly better in the combination therapy group compared with the eleuthero-alone group.¹⁶⁰

Asian Ginseng (Panax ginseng)

The root and rhizome of Asian ginseng (*P. ginseng* C. A. Meyer; from the family Araliaceae) is exported primarily from Korea, China, and Japan.

Therapeutic Uses

Asian ginseng has been used to improve mental and physical stress, anemia, diabetes mellitus, fatigue, immune response, and impotence, and to prevent cancer.

Physiologic Activity

The constituents likely responsible for ginseng's adaptogen activity are triterpenoid saponins, including ginsenosides. At least 30 ginsenosides, also referred to as *panaxosides*, have been identified. Additional constituents include carbohydrates, B vitamins, and flavonoids.¹⁶¹

Dosage and Product Considerations

Ginseng extracts are standardized to 4% ginsenosides administered at 200 mg daily in divided doses. Crude powdered root has been used in dosages of 2–3 g daily. Decoctions and tea preparations also are commonly used.¹⁶¹

Safety Considerations

Adverse effects include insomnia, headache, blood pressure changes, anorexia, rash, mastalgia, and menstrual abnormalities. Large dosages can result in

gastric upset and CNS stimulation. Ginseng should be used with caution in patients with cardiovascular disease, diabetes mellitus, or acute illness. Abuse and misuse of ginseng have been described in ginseng users, and prolonged use is not recommended.¹⁶² Ginseng should not be used during pregnancy or lactation because of a lack of data and concern about its potential estrogenic effects.¹⁶³ Several potential drug interactions are listed in [Table 51–2](#).^{71,72,161}

Summary of Clinical Evidence

Five trials were included in a Cochrane review of the role of *P. ginseng* for cognition; the majority of participants were healthy with cognitive impairment or dementia. The data could not be pooled because of varied dosing regimens, outcomes, and study durations. Although ginseng improved some end points related to cognitive function, quality of life, and behavior, the overall evidence did not support its use.¹⁶⁴ A systematic review and meta-analysis of four randomized, controlled trials of ginseng taken by patients with AD in addition to standard treatments did not identify a benefit.¹⁶⁵

A systematic review and meta-analysis examined eight randomized controlled trials of ginseng in participants with type 2 diabetes mellitus or impaired glucose tolerance, including one study using American ginseng. Subjects receiving ginseng demonstrated significant improvements in fasting glucose, postprandial insulin, insulin resistance, LDL cholesterol, triglycerides, and total cholesterol values. No significant differences were found between the ginseng and control group on hemoglobin A1C, postprandial glucose, fasting insulin, or HDL cholesterol levels. Addition of ginseng to those already treated with hypoglycemic medications or insulin also showed no difference in fasting glucose levels.¹⁶⁶

For erectile dysfunction, a systematic review of seven randomized controlled trials found significant benefit with Asian ginseng, although the review noted limitations of a small sample size and trial quality.¹⁶⁷

Green Tea

Native to southeastern Asia, the tea shrub *Camellia sinensis* belongs to the family Theaceae. Tea leaves are heated immediately after harvesting, mechanically rolled and crushed, and then allowed to dry to produce green tea. Black tea is produced by allowing the leaves to wilt before they are rolled

and left in a humid environment for several hours. This process promotes fermentation and a gradual change in color to reddish-brown. Oolong, another commonly available tea, is a partially fermented tea.

Therapeutic Uses

Green tea is considered a performance enhancer because of the stimulant effect from caffeine. Green tea also has been used to prevent cardiovascular disease, cancer, and liver disorders.

Physiologic Activity

In addition to caffeine, green tea contains polyphenolic compounds including flavonols, also known as catechins, flavonoids, and phenolic acids. The most prevalent flavonols include epicatechin, epicatechin-3-gallate, epigallocatechin, and epigallocatechin-3-gallate (or EGCG). These components have antioxidant and antitumor effects.¹⁶⁸ Both catechins and caffeine may contribute to weight loss.¹⁶⁹

A Word About Weight Loss Supplements

Dietary supplements for weight loss are some of the most popular on store shelves. The ingredients change rapidly based on the latest trends or celebrity tweets; the benefits and harms of these products can differ greatly.

Garcinia cambogia

Garcinia cambogia extracts are a source of hydroxycitric acid (HCA). Both extracts or HCA acid may exert effects by delaying glucose absorption, reducing postprandial glucose levels, and decreasing appetite, although effects in human studies have been highly variable.^a Limited clinical studies of short duration or small size have had inconsistent or not clinically significant outcomes. For example, in a 12-week study, mean weight loss in the garcinia/HCA group was 1.3 pounds higher than in the placebo group, which was statistically, but not likely clinically, significant. Garcinia extracts and HCA have been associated with reports of

hepatotoxicity, hypomania, rhabdomyolysis, and other rare but serious adverse events.^{a-c} Neither product should be recommended for weight loss.

The active components in green coffee bean extract are chlorogenic acids (CGAs). Regular roasted coffee contains very little CGA. Green coffee bean extract first became wildly popular for weight loss before any substantial human research had been conducted. Since then, a few small trials have examined effects in both normoglycemic patients and patients with diabetes. Some have demonstrated greater weight loss compared with placebo, -5 kg in 3 months in normoglycemic overweight subjects and -2 kg in 2 months in patients with metabolic syndrome.^{d,e} Both CGA and green coffee bean extract seem to be well tolerated; few adverse effects have been reported in trials. More research is needed before either CGA or green coffee bean extract can be recommended for weight loss. Patients who choose to use these products should be educated about the maximum CGA intake of no more than -900 mg daily, the maximum used in clinical trials, and about the possibility of adverse effects from caffeine if they also are using coffee drink products.

Stimulants and “Fat Burners”

After ephedrine alkaloids were banned from weight-loss supplements, some manufacturers relabeled bottles as “ephedra free!” and substituted other sources of the ephedrine alkaloids (heartleaf, country mallow). Other stimulants often are used now. Guarana, yerba maté, cola nut, and other caffeine sources are common, as is bitter orange (*Citrus aurantium*), a source of synephrine. Bitter orange has been associated with case reports of cardiovascular events and ischemic colitis, although some research has found no cardiovascular effects.^{f-h} Stimulants may provide a little boost in weight loss, but their safety issues outweigh the small benefits.

Raspberry Ketone

Raspberry ketone (4-4(hydroxyphenyl)butan-2-one) is a flavoring agent with a structure similar to that of synephrine. Increased lipolysis and adiponectin secretion in fat cells, as well as other effects noted in both

tissue and in vivo studies, indicate promise for impact on body mass, but results from animal studies for weight loss have been contradictory.ⁱ No human clinical trials of raspberry ketone alone have been published. One patient experienced sinus tachycardia, insomnia, and “jitteriness” after 1 month of raspberry ketone use, and “shakiness” also has been reported.^j At this time, patients should be discouraged from using raspberry ketone alone or in combination supplements.

^a Semwal RB, Semwal KL, Vermak I, Viljoen A. A comprehensive scientific overview of *Garcinia cambogia*. *Fitoterapia*. 2015;102:134–148.

^b Corey R, Werner KT, Singer A, et al. Acute liver failure associated with *Garcinia cambogia* use. *Ann Hepatol*. 2016;15(1):123–126.

^c Cotovio G, Oliveira-Maia A. Hypomania induced by a *Garcinia cambogia* supplement. *Austral NZ J Psychiat*. 2017;51(6):641–642.

^d Thom E. The effect of chlorogenic acid enriched coffee on glucose absorption in healthy volunteers and its effect on body mass when used long-term in overweight and obese people. *J Intl Med Res*. 2007;35:900–908. doi: 10.1177/147323000703500620

^e Roshan H, Nikpayam O, Sedaghat M, Sohrab G. Effects of green coffee extract supplementation on anthropometric indices, glycaemic control, blood pressure, lipid profile, insulin resistance, and appetite in patients with the metabolic syndrome: a randomised clinical trial. *Brit J Nutr*. 2018;119:250–258. doi: 10.1017/S0007114517003439

^f Gange CA, Madias C, Felix-Getzik EM, et al. Variant angina associated with bitter orange in a dietary supplement. *Mayo Clin Proc*. 2006;81:54518.

^g Sultan S, Spector J, Mitchell RM. Ischemic colitis associated with use of a bitter orange-containing dietary weight-loss supplement. *Mayo Clin Proc*. 2006;81:1630–1631.

^h Stohs SJ, Preuss HG, Shara M. The safety of *Citrus aurantium* (bitter orange) and its primary protoalkaloid *p*-synephrine. *Phytother Res*. 2001;251421–428.

ⁱ Cotten BM, Diamond SA, Banh T, et al. Raspberry ketone fails to reduce adiposity beyond decreasing food intake in C57BL/6 mice fed a high-fat diet. *Food Function*. 2017;8(4):1512–1518. doi: 10.1039/c6fo01831a

^j Takematsu M, Smith SW, Hoffman RS, et al. Berries that weren't that sweet after all. A case of raspberry ketone intoxication. *Clin Toxicol*. 2013;51:284.

Dosage and Product Considerations

Dosages of green tea in epidemiologic studies vary between 1 and 10 cups daily. The preferred dosage is 3–5 cups daily, or up to 1200 mL daily, including a minimum of 250 mg daily of catechins.¹⁷⁰ Green tea extract supplements are standardized to polyphenol content and retain effects similar to those of green tea while reducing exposure to caffeine.¹⁶⁸

Safety Considerations

Despite its lower caffeine content, ingestion of large quantities of green tea can cause adverse GI symptoms as well as CNS and cardiac stimulation. One 8-ounce cup of green tea contains 25–29 mg of caffeine. In comparison, an 8-ounce cup of black tea has 25–48 mg of caffeine, and an 8-ounce cup of coffee can contain 95–165 mg on average.¹⁷¹ Green tea should be avoided if other stimulating drugs are being ingested. Green tea extracts have been associated with liver toxicity,¹⁷² and serum folate levels have been reduced by green tea.⁷² As a result, green tea should be used cautiously during pregnancy and lactation because of concerns about caffeine consumption and potential concerns about folic acid. Green tea contains small amounts of vitamin K, which in large dosages may antagonize the effects of warfarin; however, catechins and caffeine also may have antiplatelet effects.⁶⁸

A Word About Kratom

Leaves of the Southeast Asian tree kratom (*Mitragyna speciosa*) historically were used for pain treatment, but current use is primarily

recreational. Two major alkaloids, mitragynine and 7-hydroxymitragynine, are mu opioid receptor partial agonists and also affect kappa and delta receptors. Kratom is psychoactive with both stimulant and opioid-like effects; heroin addicts sometimes will substitute kratom use, although it also is highly addictive.^a Illegal in a number of countries, kratom is a recreational drug option in the United States and easily obtainable in smoke and vape shops as an “herbal incense.” Although many adverse events are associated with multidrug use, reports of adverse events when kratom is used alone are growing and include increased blood pressure, impaired cognition, cardiac arrest and arrhythmias, seizures and Torsades de Pointes unresponsive to naloxone, primary hypothyroidism, liver and kidney failure, respiratory depression, coma, and death.^{b–d} More kratom-associated deaths occur when use is combined with other stimulant or depressant drugs, such as the combination of O-desmethyl and tramadol called “krypton.”^a A number of drug–drug interactions are possible, because kratom inhibits several CYP450 isoenzymes as well as P-glycoprotein transport. No published human trial studies have examined kratom use for pain or addiction treatment, although heroin addicts in Malaysia report substituting kratom.

^a White CM, Pharmacologic and clinical assessment of kratom. *Am J Health-System Pharm.* 2018;75(5):261–267. doi: 10.2146/ajhp161035.

^b Cinosi E, Martinotti G, Simonato P, et al. Following “the roots” of kratom (*Mitragyna speciosa*): the evolution of an enhancer from a traditional use to increase work and productivity in Southeast Asia to a recreational psychoactive drug in western countries. *BioMed Res Int.* 2015;2015:968786. doi: 10.1155/2015/968786. Epub 2015 Nov 10.

^c Ulbricht C, Costa D, Dao J, et al. An evidence-based systematic review of kratom (*Mitragyna speciosa*) by the Natural Standard Research Collaboration. *J Dietary Suppl.* 2013;10(2):152–170.

^d Post S, Spiller HA, Chounthirath T, Smith GA. Kratom exposures reported to United States poison control centers: 2011–2017. *Clin Toxicol.* 2019;20:1–8. doi: 10.1080/15563650.2019.1569236.

Summary of Clinical Evidence

Epidemiologic data suggest that daily consumption of green tea may protect against cardiovascular and metabolic diseases. Green and black teas were evaluated for primary prevention of cardiovascular disease by the Cochrane Heart Group.¹⁷³ Seven randomized, controlled trials were included with green tea or green tea extract as intervention for at least 3 months. A significant reduction in TC and LDL-cholesterol levels was noted, as well as small reductions in mean SBP and DBP. Cardiovascular events were not reported, presumably because of the short trial durations. Another meta-analysis of nine studies evaluating green tea's effect on cardiovascular and ischemia-related diseases found that those consuming green tea had significantly less risk of developing cardiovascular disease, intracerebral hemorrhage, or cerebral infarction compared with controls. The risk of myocardial infarction and stroke was lower in those consuming 1–3 cups versus consumption of less than 1 cup per day. In addition, those consuming high amounts, more than 10 cups per day, had significantly lower LDL cholesterol levels than those drinking fewer than 3 cups per day.¹⁷⁴ A Cochrane review found that green tea products had no significant effects for weight loss and weight maintenance in obese patients.¹⁶⁹

The consumption of green tea has been studied with regard to reducing the incidence of breast, prostate, lung, bladder, ovarian, digestive, and oral cancers. A Cochrane review of 51 studies that included 1.6 million subjects found conflicting evidence that green tea consumption affects overall cancer prevention.¹⁷⁰ Although some evidence has suggested a positive effect on prostate, lung, pancreatic, and colorectal cancers, many studies were observational in nature and performed in Asia where green tea consumption is high.

Kidney, Urinary Tract, and Prostate

African Plum

African plum is derived from the bark of *Prunus africana*, a member of the Rosaceae family.

Therapeutic Uses

Pygeum (African plum tree) bark has been used to treat benign prostatic hyperplasia (BPH).

Physiologic Activity

Pygeum bark contains phytosterols; triterpenoid pentacyclic acids, including ursolic and oleanic acids; and alcohols including docosanol. Pygeum may compete with androgen precursors and inhibit prostaglandin synthesis in the prostate. It appears to exhibit anti-inflammatory properties, inhibition of 5-alpha reductase, and reduction in concentrations of prolactin and prostate cholesterol, a precursor to testosterone synthesis.¹⁷⁵

Dosage and Product Considerations

Products are standardized to contain 14% triterpenes; the average dosage is 100 200 mg daily.¹⁷⁵

Safety Considerations

Adverse effects include diarrhea, constipation, and gastric pain. Men presenting with prostate symptoms should contact their HCP before starting pygeum to rule out prostate cancer. It is unclear if pygeum decreases prostate-specific antigen (PSA) concentrations.

Summary of Clinical Evidence

Pygeum has improved urinary flow, void volumes, residual volumes, nocturia, daytime frequency of urination, and subjective symptom assessments of BPH. Larger studies that include standardized dosages, active comparisons, and adequate durations are needed to fully assess its efficacy.¹⁷⁶

Cranberry

Cranberry (*Vaccinium macrocarpon*) is an evergreen bush native to North America and belongs to the family Ericaceae.

Therapeutic Uses

Cranberry has been used to prevent and treat urinary tract infections (UTIs).

Physiologic Activity

Cranberry contains proanthocyanidins; epicatechin is the primary proanthocyanidin found in cranberry extracts. Evidence suggests that cranberry blocks bacteria, *Escherichia coli*, in particular, from adhering to bladder, kidneys, and urethra. Fructose found in cranberry juice also may alter bacterial adhesion.¹⁷⁷

Dosage and Product Considerations

Many studies have used unsweetened cranberry juice. Cranberry juice cocktail is about 30% pure cranberry juice and contains sugar; it is unknown if this product will demonstrate the same effects. Efficacy may be based on the proanthocyanidin content. For prevention of UTI, the dosage of cranberry juice is 300–900 mL daily. Encapsulated cranberry formulations at a dosage of about 400 mg twice daily may be preferred to avoid the sugar content of juices.

Safety Considerations

Evidence suggests that regular use of cranberry concentrate tablets might increase risk of kidney stones. Patients may experience diarrhea with large doses (>3 L daily) of cranberry juice.⁷¹ Theoretically, cranberry juice may alter excretion of weakly alkaline drugs or neutralize effects of antacids. Case reports have suggested cranberry may cause bleeding in patients taking antithrombotic agents; pharmacokinetic and pharmacodynamic evidence has not supported this finding.^{72,178}

Summary of Clinical Evidence

A Cochrane review of 24 studies, with 13 included in a meta-analysis, concluded preventive use of cranberry products does not significantly reduce the overall risk of UTIs; nor is risk reduced in subgroups of women or children with recurrent UTIs, older adults, pregnant women, cancer patients, and catheterized patients. The long-term use of cranberry, specifically juice, is not well tolerated, potentially resulting in high dropout rates in studies.¹⁷⁹ An

additional consideration with negative studies is whether the tablet or capsule products contained adequate proanthocyanidins to be effective; ongoing studies are evaluating this relationship.¹⁸⁰ A subsequent systematic review and meta-analysis of UTIs in healthy women with recurrent infections found an overall 26% reduction in risk.¹⁸¹ Results from randomized, controlled studies published since the Cochrane review have been mixed as to cranberry's usefulness in preventing high-risk patients from UTIs in long-term care settings.^{182,183} Use of cranberry instead of antibiotics to prevent UTIs may be beneficial in reducing antibiotic resistance. Evidence to support cranberry products for the treatment of a current UTI is lacking; instead patients should be referred to their health care provider for diagnosis and treatment.¹⁸⁴

Dehydroepiandrosterone

Therapeutic Uses

Dehydroepiandrosterone (DHEA) is a steroid prehormone secreted by the adrenal cortex that declines with advancing age. Transformation to androgens and estrogens occurs in peripheral tissues and is regulated both systemically and locally.¹⁸⁵ DHEA dietary supplements are marketed to treat sexual dysfunction or improve sexual performance, to combat physical and mental symptoms of aging, and to enhance athletic performance or increase muscle mass.

Physiologic Activity

In general, exogenous use of DHEA in women increases testosterone concentrations to a higher level than those of estrogen, whereas the reverse is true in men. The extent to which androgen and estrogen transformation occurs depends largely on a patient's baseline concentrations of the hormones. In women, route of administration and menopausal status affect transformation; more androgens than estrogens are formed in postmenopausal women.¹⁸⁶ DHEA also has effects on nuclear receptors, stimulating osteoblastogenesis and inhibiting IL-6, which are involved in bone catabolism.¹⁸⁷

Dosage and Product Considerations

For most uses, the DHEA dosage is 25–100 mg once daily. Because of greater

risk of serious adverse effects with dosages higher than 25 mg, patients should use larger dosages only under the supervision of healthcare provider.¹⁸⁸

Although most DHEA products are synthetic, animal-extracted products exist but should be avoided because of contamination risks. Wild yam products are falsely promoted as DHEA or hormone precursors, because wild yam contains diosgenin. This hormone was once used by pharmaceutical manufacturers to produce estrogens and androgens, but the necessary chemical reactions do not occur in vivo. Some wild yam plants do contain very small amounts of naturally occurring DHEA, further complicating the patient education process for this hormone.

Safety Considerations

Adverse effects are sex hormone–related. Women may experience hirsutism, voice deepening that is generally irreversible, increased acne severity, and menstrual changes, whereas men may experience gynecomastia, reduced sperm count, and testicular changes. If hormone-associated adverse effects appear, DHEA use should be discontinued. Other adverse effects include increases in liver function enzymes, possible decreases in HDL cholesterol, as well as prostate growth, headache, nasal congestion, and insomnia.¹⁸⁹ At least four reports of mania requiring hospitalization exist; DHEA is contraindicated in bipolar disorder and should be avoided in any mood disorder.¹⁸⁸ DHEA should be avoided by patients who have a history of hormone-sensitive cancer, are taking hormonal or hormone-blocking medications, or are pregnant or lactating.

Summary of Clinical Evidence

Low DHEA levels have been associated with a greater risk of erectile dysfunction. The evidence for effectiveness of DHEA supplementation for ED is contradictory. In two trials, improvement was noted when ED was due to hypertension or unknown causes, but not when it was caused by diabetes mellitus or a neurologic condition.¹⁹⁰

A 2017 meta-analysis included 38 studies that investigated DHEA's effects on sexual function using a variety of measurements, such as the Female Sexual Function Index, International Index of Erectile Function, and Derogatis Interview Sexual Functioning Inventory.¹⁹¹ Conclusions of the analysis were

that oral DHEA supplementation does not improve sexual function in healthy men or premenopausal women, but peri- or postmenopausal women may experience improved sexual function that includes decreased dyspareunia and increased lubrication, arousal, frequency, and ability to orgasm. Although dosages of 50–100 mg/day were used, as little as 10 mg daily was found to be effective, with patients experiencing improvement similar to that found with hormone therapy treatment.¹⁹²

In addition to sexual effects, low DHEA levels may be associated with decreased bone mineral density (BMD), higher fasting glucose levels, ischemic heart disease, and all-cause mortality in older men and women.¹⁸⁵ A pooled analysis of four trials concluded that DHEA treatment increased spine BMD in women but not in men.¹⁹³ Increases from baseline averaged –1% at 1 year, with some patients experiencing increases up to 1.8% at 2 years.¹⁹³ Body composition and strength were improved more in women than men, and greater improvement was seen when treatment was combined with exercise. Some participants had improved skin health, such as increased epidermal thickness and sebum production and decreased tearing. Topical use also may benefit aging skin.¹⁹⁴

Saw Palmetto

Saw palmetto (*Serenoa repens*), a dwarf palm tree from the Arecaceae family, is native to the southeast coastal region of the United States.

Therapeutic Uses

Saw palmetto has been used to treat BPH.

Physiologic Activity

The lipophilic extracts from the ripened fruit contain fatty acids and glycerides, plant sterols and sitosterol derivatives. Saw palmetto inhibits 5-alpha-reductase and cytosolic androgen receptor binding; it also has local antiestrogenic and anti-inflammatory effects on the prostate and bladder. It does not reduce PSA concentrations.¹⁷⁵

Dosage and Product Considerations

The usual dosage is 160 mg twice daily or 320 mg once daily. Saw palmetto products should contain 80%–95% standardized fatty acids.

Safety Considerations

In comparative studies, saw palmetto was better tolerated than finasteride and tamsulosin. Mild GI complaints, along with fatigue and headache, were the most commonly reported symptoms.¹⁹⁵ Significant bleeding has been reported with saw palmetto, so its use in individuals taking antithrombotic agents should be avoided.⁷¹ Patients taking androgenic drugs also should avoid its use. Men with prostate symptoms should contact their provider to rule out prostate cancer before starting saw palmetto. Saw palmetto is occasionally used in multi-ingredient products intended for women. Because of the inhibition of 5-alpha-reductase, it is absolutely contraindicated in pregnancy and also should not be used in lactation.

Summary of Clinical Evidence

In a Cochrane review of 32 randomized controlled trials ranging from 4 to 72 weeks and involving more than 5000 men, saw palmetto was not effective for treating urinary symptoms, increasing peak urine flow, or reducing prostate size.¹⁹⁶ The meta-analysis included two high-quality trials of 582 men; data analysis based on the American Urological Association Symptom Score Index demonstrated no difference in lower urinary tract symptoms for those taking saw palmetto compared with placebo. A 72-week study at 2–3 times the usual dose of 320 mg daily found insignificant differences in lower urinary tract symptoms, including nocturnal symptoms. Three high-quality trials assessing peak urine flow in 667 men also found no change compared with placebo. No difference was noted in prostate size after a 12-month trial. Overall, the evidence does not support use of saw palmetto for BPH symptoms. Preliminary data for the effects of a combination product containing saw palmetto, lycopene, and selenium appear to be noninferior to tadalafil's effect on lower urinary tract symptoms.¹⁹⁷ Higher-quality studies are needed to further assess saw palmetto's benefit.

Musculoskeletal System

Glucosamine and Chondroitin

Therapeutic Uses

Glucosamine and chondroitin commonly are used together in supplements for osteoarthritis (OA) and joint health.

Physiologic Activity

Both glucosamine, an endogenous monosaccharide precursor to glycoaminoglycans, and chondroitin sulfate, a glycoaminoglycan, serve as “building materials” for cartilage production, but each has additional mechanisms of action. Glucosamine stimulates chondrocytes to produce cartilage and synoviocytes to produce synovial fluid and hyaluronic acid, inhibits matrix metalloproteinase, and modulates activities of inflammatory cytokines.¹⁹⁸ Cell studies have demonstrated that glucosamine also stimulates osteoblast proliferation, although it remains to be seen if the effect is significant in vivo.¹⁹⁹

Chondroitin sulfate inhibits leukocyte elastase, an enzyme involved in cartilage degradation, and bone resorption by osteoclasts; stimulates chondrocytes; reduces inflammation via inhibition of the translocation of nuclear factor kappa (involved in activating B cells); and donates sulfur, essential for the sulfur bonds used in cartilage synthesis.²⁰⁰

An in vivo pharmacoproteomics study determined that glucosamine and chondroitin used together have additional synergistic benefits on cartilage metabolism.²⁰¹ A meta-analysis of clinical studies has concluded that long-term use of both glucosamine sulfate and chondroitin can slow progression of cartilage degradation in knee OA.²⁰²

Dosage and Product Considerations

The dosage for OA is 1500 mg of glucosamine and 1200 mg of chondroitin sulfate daily taken either once or in divided doses. For larger individuals, the dosage is 2000/1600 mg; surpassing this dosage provides no additional

benefit. If glucosamine monotherapy is desired, only the sulfate salt should be used; evidence does not support use of glucosamine hydrochloride monotherapy.^{203,204} The daily dosages for glucosamine sulfate, glucosamine hydrochloride, or chondroitin monotherapy are the same when used in combination therapy. Products should be taken with food if nausea or GI upset occurs.

Neither glucosamine sulfate, chondroitin sulfate, nor their combined use will provide pain relief as quickly as ibuprofen or acetaminophen, so concurrent analgesics should be continued as needed. Effects may not be experienced for 6–8 weeks, with full benefits not evident for 4–6 months. If no benefits are noted after 6 months of therapy, it should be discontinued.

Both glucosamine sulfate and chondroitin sulfate are available in prescription-grade forms in Europe; these products have demonstrated much greater success in clinical trials, and chondroitin is considered a symptomatic slow-acting drug in OA (SYSADOA).²⁰⁰ Although these products are recommended, U.S. patients usually have to purchase them on the internet. Widely available dietary supplement products are of lower quality; expectations of the degree of effectiveness with treatment should be correspondingly lower. Patients using dietary supplement glucosamine and/or chondroitin should be counselled to purchase only products that display the USP Verified seal or were tested by a similar laboratory, or that were used in successful clinical trials.

Safety Considerations

Adverse effects for both components include mild GI upset, nausea, diarrhea, and constipation, which can often be alleviated by taking divided doses with meals. Drowsiness, headache, and skin reactions have been reported infrequently with glucosamine, whereas allergic reactions, edema, and hair loss have been reported with chondroitin sulfate. Chondroitin often is produced from bovine or porcine trachea, so there is a slight microbial contamination risk. Because trachea contains little neural tissue, risk of bovine spongiform encephalitis is minimal. Some newer sources of chondroitin do include fish or shark cartilage, so patients with severe shellfish allergies should ensure products are mammalian sourced.²⁰⁵

Glucosamine is manufactured from shellfish chitin or produced synthetically.

Some products claim to be allergen-free, because processing removes allergenic material. Two studies tested this claim using shellfish-derived products and found no reactions in individuals with documented shellfish allergies.²⁰⁶ Because source materials may not remain consistent even for a particular manufacturer, patients with severe shellfish allergies should avoid use of glucosamine and instead use bovine or porcine chondroitin monotherapy.

Pregnant or lactating women should avoid both glucosamine and chondroitin, because safety data are lacking. There are no known drug interactions for either supplement.

Summary of Clinical Evidence

Glucosamine sulfate, glucosamine hydrochloride, and chondroitin sulfate have been examined separately, with varying results for all three supplements. OA treatment guidelines from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis include pharmaceutical grade crystalline glucosamine sulfate as first-line therapy for knee OA.²⁰⁷ Other organizations, such as the European League Against Rheumatism and the American College of Rheumatology, do not distinguish activities of the supplements and consider their benefits as not clinically significant.²⁰⁸ A 2018 meta-analysis of multiple long-term treatments for knee OA included six trials of glucosamine sulfate; investigators determined that its use was associated with decreased pain in both the initial analysis and after studies with a high risk of bias were excluded, with an SMD of -0.29 (95% CI -0.49 to -0.10).²⁰⁹ For comparison, the SMD for celecoxib was -0.18 . A determination of effectiveness using surface under the cumulative ranking (SUCRA) curve methodology ranked glucosamine as most likely to be effective, with a SUCRA mean of 0.92 (95% CI 0.59 – 1.00). Hyaluronic acid plus triamcinolone ranked second at 0.88 and celecoxib third at 0.79 . A second 2018 meta-analysis included 18 trials.²¹⁰ Analysis of VAS pain scores for glucosamine determined a small effect size of -0.19 (95% CI -0.36 to -0.03) and a nonsignificant effect size of -0.04 (95% CI -0.13 to 0.06) on Western Ontario and McMaster Arthritis Index (WOMAC) scores. The Japanese Knee Osteoarthritis Measurement indicated a more favorable impact on quality of life, with an effect size of -0.73 (95% CI -1.13 to -0.32).

Benefits of glucosamine sulfate treatment may extend beyond symptom

reduction; patients who participated in two 3-year studies of a pharmaceutical grade crystalline glucosamine sulfate product and were followed for 5 years experienced a 57% reduction in the number of patients needing knee joint replacement, compared with placebo.²⁰⁷

Chondroitin monotherapy has been shown to decrease degradation rates of knee cartilage.²¹¹ A 2018 trial of 6 months duration in 604 patients compared pharmaceutical grade chondroitin with celecoxib and placebo.²¹² The pain reduction scores on a 100 mm VAS were -42.6 mm, -39.5 mm, and -33 mm in the chondroitin ($P = 0.001$), celecoxib ($P = 0.009$), and placebo groups, respectively. A 2019 meta-analysis including 18 trials in knee OA compared the SMD of pain with Lequesne index scores.²¹³ The overall effect size for pain was -0.18 (95% CI -0.25 to -0.12) but increased to -0.25 (95% CI -0.34 to -0.16) for trials using pharmaceutical grade chondroitin. Chondroitin had a greater impact on functionality; the effect size determined by the Lequesne index was -0.28 (95% CI -0.39 to -0.18) for all trials, and -0.33 (95% CI -0.47 to -0.20) for those using pharmaceutical grade chondroitin. The European League Against Rheumatism recommends chondroitin to reduce pain and to increase function in hand OA.²¹⁴

The greatest benefits may be achieved with combination of either salt of glucosamine with chondroitin. One trial of 606 patients with knee OA of moderate to severe pain compared glucosamine hydrochloride/chondroitin sulfate, 500/400 mg taken 3 times daily, with celecoxib 200 mg daily for 6 months.²¹⁵ The WOMAC scores for pain, stiffness, and function were decreased similarly at 6 months in the glucosamine hydrochloride/chondroitin and celecoxib groups, respectively: 51.1% versus 50.2%, 46.9% versus 49.2%, and 45.5% versus 46.4%. The patient or physician global assessments were similar in the groups. In the first month, rescue medications were used more often by the glucosamine hydrochloride/chondroitin group. After that period, use of rescue medications was similar between the groups.

The question of whether glucosamine sulfate/chondroitin sulfate is more efficacious than glucosamine hydrochloride/chondroitin sulfate was addressed in an open label noninferiority trial in 909 participants with mild to moderate OA. The interventions were glucosamine sulfate/chondroitin sulfate given once daily (Artrolive 1500/1200 mg sachet) or 3 times daily (Artrolive 500/400 mg capsules) compared with glucosamine hydrochloride/chondroitin sulfate (Cosamin DS 500/400 mg capsules) given 3 times daily for 16 weeks.²¹⁶ At study

end, all treatment groups had achieved significant reductions from baseline in the pain VAS ($P = 0.001$), Lequesne Index scores ($P = 0.001$), and patient and physician global assessment VAS (both $P < 0.05$), with no differences noted between groups.

Current research supports that chondroitin sulfate combined with either salt of glucosamine, chondroitin sulfate monotherapy, and crystalline glucosamine sulfate monotherapy, but not glucosamine hydrochloride monotherapy, should be considered options for treatment of patients with mild to moderate OA symptoms.

Methylsulfonylmethane

Therapeutic Uses

Methylsulfonylmethane (MSM) occurs naturally in foods and is a major metabolite of dimethylsulfoxide (DMSO), an industrial solvent. Arthritic workers began using DMSO topically, and MSM was developed in an attempt to avoid DMSO's toxicity and unpleasant side effects.²¹⁷

Physiologic Activity

Intestinal bacteria break down MSM to release sulfur, which is then incorporated into amino acids such as cysteine. Sulfur is essential for cartilage bonding; animal studies have found lower levels of sulfur in arthritic cartilage. Preclinical studies have demonstrated anti-inflammatory effects such as reduced production of IL-6 and TNF α , decreased COX-2 expression, and inhibition of nuclear factor kappaB.²¹⁸

Dosage and Product Considerations

OA dosages used in clinical trials have varied from 1500 to 3000 mg daily in 1 dose or divided doses.²¹⁹ A patient choosing to use MSM should not exceed 3000 mg daily. MSM can be destroyed by water or excessive heat during manufacture or storage, so purchasing from a reliable manufacturer and storing the product properly are essential. It is common to see smaller doses of MSM in combination products for OA; these products may not offer benefit, but they are not known to present a hazard.

Safety Considerations

Adverse effects include headache, pruritus, nausea, and diarrhea. Use in pregnancy and lactation should be avoided because of a lack of safety information. No drug interactions are known.

Summary of Clinical Evidence

A placebo-controlled pilot trial of 50 patients with knee OA noted greater improvement with MSM.²¹⁹ More recently, MSM 1.125 g given 3 times daily was compared with placebo for 12 weeks in a trial of 40 patients with knee OA.²²⁰ Reductions in WOMAC pain, stiffness, and function scores, and Aggregated Locomotor Function (ALF) scores were significantly better than placebo at 12 weeks ($P = 0.05, 0.01, 0.01$, and 0.00 , respectively), although pain VAS scores were similar. The data analyses accounted for differences between study groups at baseline in body mass index and ALF scores, which were higher in the MSM group.

MSM is used most often in combination with other supplements. One 12-week trial in 118 participants compared MSM with glucosamine sulfate, placebo, and the combination of MSM and glucosamine; significant improvement in pain and functioning was reported by all groups but placebo. Improvement was greater in the combination group than with MSM or glucosamine alone.²¹⁹ A trial in 147 patients compared glucosamine sulfate/chondroitin sulfate (1500/1200 mg daily) with glucosamine sulfate/chondroitin sulfate/MSM (1500/1200/500 mg daily) and with placebo for 12 weeks.²²¹ At the end of the study, improvements in the WOMAC scores differed significantly between groups ($P = 0.03$) at week 12, whereas only the glucosamine sulfate/chondroitin sulfate/MSM group showed significant improvement from baseline (decrease from 34.16 to 22.04, $P = 0.01$). Improvements in the VAS for pain followed a similar pattern. However, the evidence is insufficient to recommend MSM alone or in combination with other therapies.

S-adenosyl-L-Methionine (SAME)

Therapeutic Uses

S-Adenosyl-L-methionine (SAME) is an endogenous substance formed from L-methionine and ATP. SAME is marketed for OA and depression.

Physiologic Activity

SAMe is produced primarily in the liver. Liver disease and low levels of vitamin B₁₂ or folate may decrease SAMe concentrations.²²² For OA, SAMe stimulates chondrocytes to produce proteoglycans, reduces cartilage degradation enzymes such as matrix metalloproteinase-3 in serum and synovial fluid, and has anti-inflammatory effects such as decreased TNF α and IL-1 β .^{222,223}

SAMe donates methyl groups to neurotransmitters and catecholamines and thereby increases brain neurotransmitter levels, including those of norepinephrine, dopamine, and serotonin, which may contribute to antidepressant effects.

Dosage and Product Considerations

Most OA trials used dosages of 400–800 mg daily in divided doses, whereas dosages for depression are 1200–1600 mg daily.²²⁴

Safety Considerations

Adverse effects include nausea, diarrhea, and heartburn. Less frequently, dry mouth, headache, dizziness, nervousness, insomnia, cognitive impairment, and a switch to mania in patients with bipolar disorder have been reported.²²⁴

SAMe also is associated with hypomania or severe mania in subjects who have no personal or family history of mania or bipolar disorder; a report of mixed mania with suicidal ideation occurred within 2 weeks of its use.^{224,225} These CNS effects may be dose related, because mania and hypomania have been reported with the higher dosages used for depression but not with the lower dosages used in OA trials. Patients who use SAMe for OA should take the lowest dosage that provides relief but no more than 800 mg daily.

Use in pregnancy or lactation should be avoided. Potential drug interactions are listed in [Table 51–2](#).

Summary of Clinical Evidence

Many early OA trials with positive results were of short duration and poor design, and they used injectable dosage forms or combinations of intravenous and oral therapies.²²⁶ When oral SAMe was compared with NSAIDs or a COX-2

inhibitor, equivalent results in restoration of functionality and decreased pain were seen, although with slower onset.²²⁷ A more rigorously designed trial compared SAME (1200 mg daily) with nabumetone.²²⁸ Pain measured on a 40-mm VAS showed a significant decrease to a similar extent in the SAME (–13 mm) and nabumetone (–15.7 mm) groups at 8 weeks. The WOMAC index also decreased similarly in the SAME and nabumetone groups (–6.9 mm and –9.3 mm, respectively; $P = 0.459$). However, the changes occurred more slowly in the SAME group. A meta-analysis concluded that SAME's clinical effects may be small.²²⁶ Because of the limited evidence and the severity of possible adverse effects, use of SAME should not be recommended.

Turmeric/Curcumin

The names *curcumin* and *turmeric* often are used interchangeably, especially for the spice used in cooking, but curcumin is the primary curcuminoid present in the turmeric plant (*Curcuma longa*).²²⁹

Therapeutic Uses

Turmeric extracts and curcumin are used primarily for arthritis and inflammatory conditions.

Physiologic Activity

Curcumin has anti-inflammatory activity via inhibition of arachidonic acid metabolism, lipooxygenase, COX, TNF α , and interleukins.²²⁹ It also decreases expression of matrix metalloproteinase-3.²³⁰ In a study of patients with knee OA, turmeric extract 90 mg daily decreased COX2 secretion into synovial fluid similarly to diclofenac 75 mg daily.²³¹ Curcumin extracts have antihyperlipidemic, antitumor, antibacterial, antioxidant, and antidiabetic effects. Its body distribution is fairly low but increases when ingested with oils; researchers have developed a nanoparticle formulation with increased bioavailability.²²⁹

Dosage and Product Considerations

An optimum dosage has not been determined. Clinical trials demonstrating benefit have used 1000–1500 mg daily in divided doses.

Safety Considerations

The most common side effects are GI discomfort and nausea. Human studies show good tolerance with dosages as high as 12,000 mg daily.²²⁹ Curcumin inhibits platelet aggregation, so patients on antithrombotic agents should use curcumin cautiously.

Summary of Clinical Evidence

A noninferiority trial ($n = 367$) compared 1500 mg of turmeric extract daily to 1200 mg of ibuprofen daily for 4 weeks.²³² The WOMAC total, pain, stiffness, and function scores were all similar between the turmeric and ibuprofen groups; 64.3% and 63.8% of turmeric and ibuprofen patients, respectively, rated themselves as “improved” on the global assessment. Adverse events were similar except for less abdominal pain/distention in the turmeric group, (10.8% vs. 18.1%, $P = 0.046$). Similar results were observed in a study comparing 500 mg curcumin 3 times daily to 50 mg daily of diclofenac in 139 patients.²³³ All scores on the Knee Injury and Osteoarthritis Outcome Score improved similarly; pain subscores decreased from 53.29 to 35.48 and 53.15 to 37.23 in the curcumin and diclofenac groups, respectively. Adverse events were mild, occurring in 13% of the curcumin group and 38% of the diclofenac group. Curcumin-treated patients experienced significantly less flatulence ($P < 0.01$) than patients taking diclofenac and a greater decrease in weight, 1.01 kg vs. 0.12 kg ($P < 0.01$).

A polysaccharide-rich turmeric extract was examined in an OA trial in 120 patients.²³⁴ Patients were randomized to receive 500 mg turmeric extract, 750 mg glucosamine sulfate, curcumin extract/glucosamine sulfate, or placebo, each twice daily for 42 days. The VAS pain scores were reduced significantly from baseline in all groups, with the greatest change in the turmeric group, decreasing from 66.5 to 19.48 ($P < 0.01$). WOMAC scores also were improved in the turmeric group, decreasing from 54.97 to 17.14 ($P < 0.01$). Pain and WOMAC score reductions for glucosamine also were significantly better than baseline, but less so than those for turmeric. Combination treatment was less effective than either treatment alone, so no synergistic or additive effect was demonstrated.

The evidence for curcumin/turmeric is supportive, especially in light of its favorable safety record. It may be an appropriate option for some patients with

mild osteoarthritis symptoms.

Skin Conditions

Aloe Vera

Aloe vera or *Aloe barbadensis*, commonly called “aloe vera,” is a succulent perennial, endemic to desert regions. Found in the leaf mucilage is a viscous, clear gel that has been historically used since ancient Egyptian times for dermatologic conditions. It is a member of the Liliaceae family, and is also known as the “desert lily.”²³⁵

Therapeutic Uses

Aloe vera gel has been used topically for wound healing, including cuts, scrapes, and minor burns. Oral aloe products had been approved as a nonprescription stimulant laxative ingredient, but this dosage form was removed in 2002 from the nonprescription drug monographs because of a lack of safety and efficacy data.²³⁶

Physiological Activity

Aloe vera gel is derived from the mucilage of the plant and contains immunostimulating polysaccharides, called glucomannan, which contribute to collagen production, stimulate fibroblast growth factor, and improve transversal connections promoting skin healing. It also is rich in vitamins E, C, amino acids, and other antioxidants. Aloe vera may have anti-inflammatory and antimicrobial effects.²³⁵ The outer skin of the plant, the latex, contains anthraquinone glycosides, including aloin, aloe-emodin, and barbaloin, which are responsible for laxative actions. Whole leaf extract contains both mucilage and latex.²³⁷

Dosage and Product Concerns

Aloe vera gel is applied topically 2–3 times per day for the treatment of minor cuts, scrapes, and burns. Aloe vera is a component in many beauty and nonprescription products as an inactive ingredient. The International Aloe Science Council will certify products on the basis of labeling, aloe content, aloe

source, and quality standards defined by the council. It sets criteria of less than 10 ppm of aloin for oral products and 50 ppm for topical formulations.²³⁸

Safety Considerations

Topical aloe vera generally is well tolerated, with occasional adverse effects of rashes and skin irritations, especially if the person has an allergy to members of the Liliaceae family, such as lilies, garlic, or onions. Oral administration may cause laxative effects, GI upset, hypoglycemia, or hypokalemia related to the presence of anthraquinones. Case reports of hepatotoxicity have been attributed to oral aloe use.²³⁷ Drug interactions have been reported with hypoglycemic, antiretroviral, and antithrombotic agents.⁷¹ The consumption of oral aloe should be avoided, because safety data are lacking.

Summary of Clinical Evidence

A Cochrane systematic review of randomized, controlled studies evaluated seven trials involving 347 subjects using aloe or aloe-derived products, either as topical gels or wound dressing, for wound healing. Five trials included participants with burns, hemorrhoidectomy, and skin biopsies. In a comparison of aloe with silver sulfadiazine, no difference in the duration of burn healing was noted. Healing time was significantly decreased after hemorrhoidectomy in the aloe group (RR 16.33 days [95% CI 3.46–77.15]). No difference in the completion of healing of skin biopsy sites was found. Two trials evaluating time to healing in chronic wounds found no difference or significant delay.²³⁹

An analysis of four trials comprising 371 subjects identified benefits in healing of first- and second-degree burns. Studies were combined and data analyzed using weighted mean differences (WMDs) on healing time. The WMD on the healing time was significantly decreased by 8.79 days in the aloe vera group versus the control group. Using active comparison control subjects, aloe demonstrated benefit over silver sulfadiazine and petrolatum (Vaseline) gauze. The trials were small and of variable quality.²⁴⁰

Overall, topical aloe vera is well tolerated, but evidence to support its efficacy in acute wound healing is mixed. It may be a useful adjunct to treatment in selected patients who are appropriate candidates for self-care.

Tea Tree Oil

Tea tree oil (TTO) is derived from leaves of the tree *Melaleuca alternifolia*, a member of the family Myrtaceae. The tea tree is not related to the plant used to make black and green teas.

Therapeutic Uses

TTO has been used as a topical anti-infective agent for conditions affecting skin and mucosa.

Physiologic Activity

TTO's major active component is terpinen-4-ol, which has displayed broad-spectrum antimicrobial activity against bacteria, fungus, viruses, and protozoa. Terpinen-4-ol also has demonstrated anti-inflammatory properties in decreasing TNF, IL-1, IL-8, IL-10, and prostaglandin E2. TTO constituents such as alpha-terpinene, alpha-terpinolene, and gamma-terpinene may have antioxidant properties.²⁴¹

Dosage and Product Concerns

The oil is applied topically once or twice daily in concentrations of 0.4%–100%, depending on the condition and area of treatment. For acne, a 5% concentration is applied daily. For athlete's foot, TTO solution 25%–50% is applied twice daily for 4 weeks. For fungal toenail infections, TTO 100% has been used twice daily for 6 months.

Safety Considerations

Skin irritation may occur upon topical application, especially at higher concentrations. Contact dermatitis, various skin reactions, and prepubertal male gynecomastia have been reported. Although the oil can be used safely on oral mucosa, it should not be swallowed, because its ingestion may be toxic.²⁴¹

Summary of Clinical Evidence

TTO may be effective for athlete's foot and other fungal infections of the skin,

hair (dandruff), and nails.²⁴²⁻²⁴⁴ For onychomycosis, TTO was compared with clotrimazole 1% solution; after 6 months both had similar culture and clinical resolutions.²⁴⁴ Evidence supporting TTO use for fungal conditions is older and has not been compared with current treatment options; it may be an option for individuals who are not tolerating current therapies for the treatment of athlete's foot or onychomycosis.

TTO often is an ingredient included in commercial acne products. Although evidence to support efficacy is positive, it is limited. In the treatment of mild to moderate acne, daily application of TTO gel 5% for 45 days significantly reduced the total acne lesion count and acne severity index compared with placebo.²⁴⁵ A recent open-label, phase II pilot study found TTO gel (200 mg/g) also significantly improved lesion count over 12 weeks and was well tolerated.²⁴⁶

Women's Health

Black Cohosh

Black cohosh is made from the dried rhizome and roots of *Cimicifuga racemosa*, formerly *Actaea racemosa*. It is a member of the Ranunculaceae (buttercup) family.

Therapeutic Uses

Black cohosh has been used to treat the symptoms of premenstrual syndrome, dysmenorrhea, menopause, and rheumatoid arthritis.

Physiologic Activity

The active components of black cohosh rhizomes are triterpene glycosides, including acetin, cimicifugoside, and 27-deoxyacetin. Isoflavones such as formononetin often are present, but they may be absent from commercial products. Other constituents include isoferulic and salicylic acids, tannins, resin, starch, and sugars.²⁴⁷ Black cohosh extract also may modulate serotonin.²⁴⁸ Black cohosh probably does not exhibit estrogenic activity and has no effect on vaginal epithelium, endometrium, or hormone concentrations.²⁴⁹

Dosage and Product Considerations

Black cohosh, as a standardized extract, is usually taken as 40 mg daily in 1–2 doses. One proprietary preparation is Remifemin. The extract is standardized to 1 mg of triterpene glycosides, calculated as 27-deoxyactein, per 20-mg extract tablet.²⁵⁰

Safety Considerations

Adverse effects are mild and include GI complaints, headache, rash, and weight gain. Hepatitis, seizures, and cardiovascular disease have been reported in patients taking combination products that contain black cohosh, although a causal relationship has not been established.²⁵¹ Case reports of acute hepatitis while taking black cohosh have been reported; the USP Botanical Dietary Supplements and Herbal Medicines Expert Committee recommended that a cautionary statement regarding potential hepatotoxicity be placed on product labels.²⁵⁰ Further evaluations have suggested lack of product quality may have contributed, with the wrong plant being used. The use of black cohosh for longer than 6 months is not recommended because of the lack of long-term safety studies.²⁵² Data on drug interactions with black cohosh are limited, with the exception of possible additive effects with tamoxifen.²⁵¹ Unprocessed black cohosh plants contain small amounts of salicylic acid, but its presence in commercial products is unknown. Data on concurrent use with estrogens or progestins are not available. The use of black cohosh should be avoided during pregnancy and lactation because of its potential hormonal effects.²⁵⁰

Summary of Clinical Evidence

Several clinical trials that have evaluated black cohosh alone and in combination products for menopausal symptoms reported mixed results. A systematic review of black cohosh included 16 randomized controlled trials with 2027 perimenopausal or postmenopausal women.²⁵³ Efficacy was compared against placebo, hormone therapy, red clover, and fluoxetine. Analysis found the median dose of 40 mg daily of black cohosh for a 23-week average. For hot flashes and menopausal scores, no significant difference was noted between black cohosh and placebo, whereas hormone therapy significantly reduced these outcomes. Other data provided inconclusive results as to the efficacy of black cohosh.²⁵³

Multi-ingredient product comparisons with placebo, hormonal therapy, and fluoxetine lack standardized dosing and have poor methodologic quality or small differences compared with placebo, making it difficult to establish efficacy. Benefits from other constituents in multi-ingredient products and from SJW may contribute to improvement in symptoms. Combining black cohosh with SJW has demonstrated an improvement in climacteric symptoms.²⁵⁴ The ACOG practice guideline for managing menopausal symptoms stated insufficient evidence exists to support use of natural products.²⁵⁵

The safety and efficacy of black cohosh in women who have had breast cancer remain controversial. A systematic review in women with a history of breast cancer found inconclusive evidence to support safety and efficacy, although the product did not exert estrogenic effects.²⁵⁶ A second systematic review of women with or without greater risk of breast cancer found the use of black cohosh did not increase risk of developing cancer.²⁵⁷ The long-term effects on cardiovascular disease, osteoporosis, and breast cancer are unknown.

Chasteberrys

Chaste tree (*Vitex agnus-castus*), commonly referred to as “vitex,” is a member of the Verbenaceae family. The dried ripe fruits, or berries, and the leaves are the medicinally useful parts of the plant.

Therapeutic Uses

Chasteberry has been used to treat symptoms of premenstrual syndrome (PMS), premenstrual dysphoric disorder (PMDD), dysmenorrhea, mastalgia, and menopausal symptoms.

Physiologic Activity

The fruits contain essential oils, diterpenes, iridoid glycosides, and flavonoids. Effects on menstrual regulation are likely caused by the dopaminergic compounds diterpenes, which are responsible for suppressing prolactin release by binding to the dopamine-2 receptor. Chasteberry may have weak estrogenic activity.²⁵⁸

Dosage and Product Considerations

Clinical trials have used 20–40 mg of the extract daily. The standardization of chasteberry has not been well established. It is available alone or in combination products.

Safety Considerations

GI complaints occur occasionally with use of chasteberry. Other symptoms include dry mouth, headache, rashes, itching, acne, menstrual disorders, and agitation. Chasteberry should be avoided during pregnancy because of insufficient data to support safe use and the possibility of lactation suppression. Theoretically, chasteberry may interact with medications that impact dopamine, as well as hormone replacement therapies and oral contraceptives.²⁵⁹

Summary of Clinical Evidence

Evidence for chasteberry, in combination with other herbal medicines, for menopausal symptoms is mixed. A randomized, double-blind, placebo-controlled parallel trial studied combination SJW (*H. perforatum*) and chasteberry administered twice daily over 16 weeks in 100 perimenopausal and postmenopausal women. Symptoms regarding the primary end point of hot flashes did not differ between the groups.²⁶⁰ Phyto-Female Complex, standardized extracts of black cohosh, dong quai, milk thistle, red clover, American ginseng, and chasteberry, has been studied in 50 premenopausal and postmenopausal women in a randomized, placebo-controlled trial. Improvements in hot flashes, night sweats, and sleep quality were reported, with no changes on vaginal ultrasonography, or with levels of estradiol, follicle-stimulating hormone, liver enzymes, or thyroid-stimulating hormone.²⁶¹

Chasteberry extract may be effective in PMS, PMDD, and latent hyperprolactinemia. A systematic review of seven trials of PMS found chasteberry to be more effective than placebo, pyridoxine, or magnesium. In two trials on PMDD that compared fluoxetine and chasteberry, data were conflicting, with one study showing chasteberry as effective. Chasteberry was more effective than placebo in one trial, and as effective as bromocriptine in another, for the treatment of hyperprolactinemia and associated clinical markers.²⁶² Methodologic quality has been limited by small study sizes, as well

as variability in chasteberry preparations, diagnostic criteria, and treatment measures.

Evening Primrose Oil

Evening primrose (*Oenothera biennis*) is a member of the primrose family Onagraceae and is used for its high content of essential fatty acids. The seed oils of black currant (*Ribes nigrum*) and borage (*Borago officinalis*) also are used for similar purposes.

Therapeutic Uses

Evening primrose oil (EPO) has been used for mastalgia, PMS, menopause, preeclampsia, diabetic neuropathy, chronic fatigue syndrome, and atopic dermatitis.

Physiologic Activity

The oil from evening primrose seeds consists of omega-6 essential fatty acids, primarily 65%–75% linoleic acid and 7%–10% gamma linolenic acid. These components are thought to be responsible for anti-inflammatory activity.^{263,264} The seed oil contains smaller amounts of palmitic, oleic, and stearic acids, as well as campesterol and beta sitosterol.²⁶⁴

Dosage and Product Considerations

In clinical trials, daily dosages of EPO 2–4 g have been used as a liquid or a capsule. A standardized product, Efamol, a 1 g capsule, contains 0.62 g linoleic acid, 0.05 g gamma linolenic acid, and 0.062 g oleic acid.²⁶³

Safety Considerations

Adverse effects include headache, nausea, diarrhea, and occasional abdominal pain. EPO products may possess antiplatelet effects and should be used with caution in patients taking antithrombotic agents. Seizures have been reported in people taking EPO, so individuals taking anticonvulsants should avoid its use.^{71,72} Use of EPO for cervical ripening during labor may be associated with adverse pregnancy outcomes including prolonged rupture of membranes and vacuum extraction.²⁶⁴ Use for cervical ripening is further unsupported by a

recent randomized controlled trial that also found EPO had no impact on duration of pregnancy or labor when administered at 40 weeks of gestation.²⁶⁵

Summary of Clinical Evidence

Few studies exist for the benefit of EPO on mastalgia. A randomized pilot placebo-controlled study found improvement in cyclic mastalgia with EPO 3 g, taken alone or in combination with vitamin E 1200 IU over 6 months.²⁶⁶ A large double-blind, randomized, placebo-controlled trial that compared a branded British product containing gamma linolenic acid with or without antioxidant vitamins found no significant changes in reported pain in patients with moderate to severe mastalgia. A large placebo effect was noted, with 40% of subjects reporting improvement without therapy.²⁶⁷ Another trial of 90 participants over a 2-month period compared EPO, flaxseed, and vitamin E effects on breast pain, finding only flaxseed to have a significant improvement from baseline.²⁶⁸

A Cochrane review of 19 studies using oral EPO and borage oil concluded neither was effective for the treatment of atopic eczema. Studies of EPO found no improvement in global eczema symptoms recorded by a VAS.²⁶⁹ A small randomized, placebo-controlled study conducted more recently in participants from Korea with mild atopic eczema found significant benefit in Eczema Severity Index Scores with EPO.²⁷⁰

Fenugreek

Fenugreek (*Trigonella foenum-graecum*) has a long history of use as a spice and a medicine in India, China, and Northern Africa. Both leaves and seeds may have medicinal properties.²⁷¹

Therapeutic Uses

Fenugreek has been used for diabetes mellitus, hyperlipidemia, GI conditions, and stimulation of breast milk production.

Physiologic Activity

An active constituent of fenugreek, 4-hydroxyisoleucine, may contribute to the hypoglycemic effects by stimulating glucose-induced insulin release and

reducing insulin resistance.²⁷¹ Saponins converted to sapogenins in the GI tract may decrease cholesterol levels through activation of biliary cholesterol secretion. Fenugreek seeds are high in fiber and possibly delay glucose absorption or binding of cholesterol.²⁷² Lactation effects may result from increased sweat production that impacts the milk duct or from phytoestrogens and diosgenin found in fenugreek.²⁷³

Dosage and Product Considerations

Dosages have varied, with fenugreek seed powder capsules 2.5 g twice daily or seed powder 25 g daily in 2 divided doses used in studies. Defatted seeds also have been used at 100 g daily in 2 equally divided doses. Fenugreek also can be administered in a tea.²⁷² For increasing milk supply, 2–3 capsules (580–610 mg per capsule) can be administered 3–4 times daily.²⁷³ Alternatively, seeds may be soaked in water and strained, and then the water is consumed.

Safety Considerations

Fenugreek is generally safe when used in meal preparation. When fenugreek is consumed, urine, sweat, and breast milk have been noted to smell like maple syrup, which is caused by sotolone excretion. This effect also occurs in breastfeeding infants, which has led to mistaken cases of maple syrup urine disease. Patients with an allergy to chickpeas should avoid fenugreek because of possible cross-reactivity; inhalation of the powder has resulted in bronchospasm. Fenugreek consumption in higher amounts than found in food should be avoided during pregnancy because of potential oxytocic and uterine stimulant effects. Hypoglycemia or hypokalemia may result from use. The high-fiber content can bind with oral medications and decrease absorption.²⁷² Fenugreek may impact platelet aggregation, potentially increasing risk of bleeding in patients taking antithrombotic agents.⁶⁸

Summary of Clinical Evidence

Although fenugreek is promoted to stimulate production of breast milk, evidence is limited.²⁷³ A systematic review and network meta-analysis evaluated five small studies with various comparators, including placebo, control, and other galactagogues (palm dates, *Coleus ambonicus*). Paired comparisons in four studies showed a slight, but significant, increase in milk production against placebo or control, but not when compared with other

galactogogues.²⁷⁴ Small studies of varying quality and dosages have noted potential benefit of glycemic control and dyslipidemia in patients with prediabetes and diabetes mellitus. Pooled results of 10 studies demonstrated clinically significant benefits in fasting blood glucose, 2-hour postprandial blood glucose, hemoglobin A1C, and total cholesterol, but not in triglycerides, LDL cholesterol, and HDL cholesterol. Limitations exist in methodology, sample size, duration, and dosage, and the formulation of fenugreek used.²⁷⁵

Phytoestrogens

Phytoestrogens are found in many different plants; supplements have been derived primarily from soy (*Glycine max*) and red clover (*Trifolium pratense*).

Therapeutic Uses

Phytoestrogens have been used mainly for symptoms associated with menopause and related bone health. Soy also is consumed for its potential benefits in prevention of cardiovascular disease and cancer.

Physiologic Activity

Soy-based phytoestrogens are composed of isoflavones, such as genistein, daidzein, and glycitein. Red clover-based products have greater content of the isoflavones biochanin A and formononetin.²⁷⁶ These compounds' effects include estrogenic, antiestrogenic, antioxidant, and anticancer activity.

Dosage and Product Considerations

A recommended dosage of phytoestrogen has not been established, but the majority of clinical trials include 50–100 mg daily of isoflavones.²⁴⁸ Phytoestrogen products contain varying amounts and types of isoflavones. Products derived from soy and red clover sources may have different effects; red clover isoflavones may have greater bioavailability.²⁴⁸ The benefits from soy are primarily from dietary sources, not from supplements.

Safety Considerations

Phytoestrogen products derived from soy or red clover are well tolerated. GI complaints and allergic reactions may occur. The long-term safety of

phytoestrogens is not established, especially with respect to the risk of estrogen-dependent cancers and thromboembolic disease. The safety of phytoestrogen supplements in women with hormone-sensitive cancers is unknown, and their use should be avoided.⁷¹

Summary of Clinical Evidence

Purported benefits of phytoestrogens, especially soy-based products, are derived from population-based observational studies of dietary patterns. The lifetime risk of any disease is unlikely to be related solely to the presence or absence of one dietary component such as isoflavones. The phytoestrogen content in foods, especially of the biologically active isoflavones, varies significantly, even in soy foods.

The most common use of phytoestrogens is to manage menopausal symptoms. A large meta-analysis and systematic review of 63 randomized, controlled studies and more than 6000 women evaluated the effectiveness of plant-based agents. Pooled mean differences showed that scores for daily hot flash frequency and vaginal dryness improved significantly in the phytoestrogen groups, although night sweats did not.²⁷⁷

The effect of phytoestrogens on BMD may be beneficial in women experiencing menopause, but mixed findings have been reported. A systematic review of 23 randomized, double-blind, controlled trials evaluated extracts of red clover, soy isoflavone, genistein (singularly or combined with daidzen), and dietary soy intake on BMD. Impact on bone health varied with duration of intake, as well as dosage and isoflavone content.²⁷⁸

FDA recently challenged the health claim that daily ingestion of soy protein as part of a diet low in saturated fat and cholesterol may reduce the risk of coronary heart disease. In the proposed revocation, it cites current evidence does not support this previous designation and extended an open comment period as part of its review.²⁷⁹

Epidemiologic research has indicated consumption of soy products has a role in decreasing breast cancer risk although concerns exist that estrogenic activity will increase recurrence. The potential effect likely will depend on the specific isoflavone, timing of exposure, and genetic factors, and whether estrogen receptors are positive or negative for cancer. Dietary consumption of soy similar to that in Asian populations does not appear to increase cancer

recurrence, nor does it cause interactions with tamoxifen or anastrozole.²⁸⁰ Another review concluded overall safety is promising, because endometrial, uterine, and breast cancer risk do not appear to be increased. Dietary soy intake may even be associated with a decrease in endometrial or uterine cancers; however, it should be used with caution at the present time.²⁸¹ A systematic review and a meta-analysis suggest that consumption of soy food, genistein, daidzein, and unfermented soy food may significantly reduce prostate cancer risk.²⁸²

A Word About Piperine

Piperine is the main alkaloid in black pepper (*Piper nigrum*). It demonstrates nonspecific inhibition of CYP450 enzymes and strongly inhibits P-glycoprotein, leading to increased absorption and increases in many drug concentrations.^a Piperine also inhibits bacterial efflux pumps, which could increase the effectiveness of antibiotic therapy.^b Dietary supplement manufacturers are including *Piper nigrum* extracts, piperine, or BioPerine, a patented extract, in many dietary supplements to increase absorption or to prolong effects. Patients taking these products also must consider the impact on any prescription medications. Increases in drug concentrations could be seen with many oral drugs; phenytoin concentrations were doubled in one study, whereas the area under curve of nevirapine increased by 170%.^{a,c}

^a Bhardwaj RK, Glaeser H, Becquemont L, et al. Piperine, a major constituent of black pepper, inhibits human P-glycoprotein and CYP3A4. *J Pharmacol Exp Ther*. 2002;302:645–650.

^b Khamenah B, Iranshahy M, Ghandadi M, et al. Investigation of the antibacterial activity and efflux pump inhibitory effect of co-loaded piperine and gentamicin nanoliposomes in methicillin-resistant *Staphylococcus aureus*. *Drug Devel Indust Pharm*. 2015;41(6):98994.

^c Kasibhatta R, Naidu MUR. Influence of piperine on the pharmacokinetics of nevirapine under fasting conditions. *Drugs R D*. 2007;8(6):383–391.

Assessment of Natural Product Use: A Case-

Based Approach

As stated in [Chapter 50](#), the health care provider should determine the patient's reasons for purchasing a natural product. The appropriateness of supplement use must be determined, especially for a child, a pregnant woman, or an older adult. If a medical condition is being treated and use of a supplement is appropriate, the patient should be encouraged to involve the health care provider in its use. Information about possible allergies to plant materials, current drug therapy, and comorbid conditions will identify possible contraindications. If self-treatment is appropriate, the provider should review the length of therapy and recommended dosages with the patient. Cases 51–1 and 51–2 provide examples of assessment of patients who are considering use of a natural product.

Case 51–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Information Gathering	
1. Gather essential information about the patient's symptoms and medical history, including	A patient asks you for instructions on how to use melatonin for jet lag. She is going on a work trip to Croatia next week.
a. description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	"I get horrible jet lag when I fly that far! I just can't sleep the first few days, and I really need to function better to do my job."
b. description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Patient tries to maintain good sleep habits even while traveling. She uses a sleep mask but has found ear plugs too irritating for long-term use.
c. description of the patient's efforts to relieve the symptoms	She has tried antihistamines in the past and found they left her extremely groggy.
d. patient's identity	Rachel Klebser
e. age, gender, height, and weight	36 years old female, 5 ft 5 in., 136 lb
f. patient's occupation	Location scout for fashion photography magazine

Relevant Evaluation Criteria	Scenario/Model Outcome
g. patient's dietary habits	Tries to follow a Mediterranean-style diet most of the time.
h. patient's sleep habits	Usually gets 6–8 hours of sleep per night; rarely has a sleepless night.
i. concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Endometriosis: symptoms controlled with continuous-use oral contraceptive. Takes generic multivitamin and mineral, 1 tablet daily.
j. allergies	NKDA; no known food or plant allergies
k. history of other adverse reactions to medications	None
l. other (describe) _____	Patient brings to the pharmacy counter a combination multi-herbal and melatonin product that contains 0.3 mg of melatonin.
Assessment and Triage	
2. Differentiate patient's signs/symptoms and correctly identify the patient's primary problem(s).	Patient wishes to minimize effects of air travel.
3. Identify exclusions for self-treatment.	The patient has chosen a product with an inappropriate dosage of an active ingredient and extra herbal ingredients not assessed for efficacy.
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Recommend an adequate dosage of melatonin with appropriate education on usage. (2) Recommend that the patient try a different nonprescription sleep aid. (3) Refer patient to health care provider for a prescription hypnotic. (4) Take no action.

Relevant Evaluation Criteria	Scenario/Model Outcome
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Suggest melatonin 5 mg supplement, preferably a brand that is DSVP certified or tested through another third-party laboratory.
6. Describe the recommended therapeutic approach to the patient or caregiver.	After arriving at the travel destination, take melatonin 5 mg between 5 and 10 pm. Ideally, it would be taken 30–60 minutes before attempting to sleep. Continue taking 1 tablet about 30 minutes before bedtime for the next 2–5 days.
	Continue good sleep practices such as a warm bath or shower before bed and use of a sleep mask. Consider taking your personal pillow with you. Because you cannot tolerate earplugs, you could try a portable white-noise machine to mask noises.
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	The dose of melatonin in the product she has chosen is not high enough to prevent jet lag. The multi-herbal combination has not been studied to show if it has any effect in treating jetlag and if it can increase the risk of adverse effects.
Patient Education	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	Explain that melatonin works by helping to “reset” the body's natural clock, the circadian rhythm, and probably will not cause a feeling of “sleepiness.” Side effects are uncommon but include headache and nausea. Morning drowsiness is a possibility.
Solicit follow-up questions from the patient or caregiver.	“What if this still doesn't help me get to sleep?”
Answer the patient's or caregiver's questions.	If the melatonin and additional sleep hygiene suggestions do not sufficiently help you sleep on this trip, try halving the dose of antihistamine you used previously and taking it earlier in the evening. These measures should help reduce morning grogginess. After you return, we can discuss some other options for future trips, such as use of

Relevant Evaluation Criteria	Scenario/Model Outcome
	valerian.
Evaluation of Patient Outcome	
9. Assess patient outcome.	Patient's sleep difficulties during the first days of her trip are not likely to be resolved completely, but they should be reduced to a tolerable level.

Key: DSVP = Dietary Supplement Verification Program.

Case 51-2

Relevant Evaluation Criteria	Scenario/Model Outcome
Information Gathering	
1. Gather essential information about the patient's symptoms and medical history, including	
a. description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient is inquiring, "Does this really work?" He is holding a bottle of St. John's Wort and pointing to the statement "supports emotional health."
b. description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Patient says he has been feeling "down" and "hopeless" for a few months now. He describes having low energy, and he does not want to get out of bed in the morning. Upon questioning, he tells you he does not feel suicidal.
c. description of the patient's efforts to relieve the symptoms	He has not spoken to anyone about his feelings; he is embarrassed to go see his family doctor to "talk about these things."
d. patient's identity	Samuel Jackson
e. age, gender, height, and weight	50 years old, male, 5 ft 10 in., 185 lb

Relevant Evaluation Criteria	Scenario/Model Outcome
f. patient's occupation	Welder at a large manufacturing plant
g. patient's dietary habits	Occasionally eats fast food for lunch or dinner.
h. patient's sleep habits	Not sleeping well, 4–5 hours per night; frequently wakes up.
i. concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	High blood pressure and dyslipidemia treated with lisinopril 20 mg and atorvastatin 10 mg, respectively.
j. allergies	NKDA
k. history of other adverse reactions to medications	No adverse reactions to medications
l. other (describe) _____	n/a
Assessment and Triage	
2. Differentiate patient's signs/symptoms and correctly identify the patient's primary problem(s).	The described symptoms indicate he may be suffering from depression.
3. Identify exclusions for self-treatment.	Symptoms of depression should not be self-treated, so he should be referred for evaluation, diagnosis, and treatment.
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer patient to an appropriate health care provider or mental health professional. (2) Recommend self-care with a nonprescription/dietary supplement product. (3) Recommend self-care until patient can see an appropriate health care provider. (4) Take no action.

Relevant Evaluation Criteria	Scenario/Model Outcome
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	No alternative treatment may be recommended.
6. Describe the recommended therapeutic approach to the patient or caregiver.	"You should consult a health care provider or mental health professional to discuss your symptoms and be evaluated."
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	"This option is best, because you should be evaluated, treated, and monitored to help you feel better. "
Patient Education	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	Patient is not a candidate for self-treatment.
Solicit follow-up questions from the patient or caregiver.	"Why can't I take this in the meantime?"
Answer the patient's or caregiver's questions.	"Symptoms such as yours should not be self-treated. Additionally, SJW may interact with atorvastatin."
Evaluation of Patient Outcome	
9. Assess patient outcome.	Contact the patient in a day or two to ensure that he made an appointment and sought medical care.

Key: n/a = Not applicable; NKDA = no known drug allergies; SJW = St. John's wort.

Chapter 52: Common Complementary and Integrative Medicine Health Systems

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The term *complementary and integrative medicine* (CIM) refers to a broad domain of healing practices that include diverse health systems, modalities, and practices, and their accompanying theories and beliefs.¹⁻³ CIM includes many modalities beyond simply the use of dietary supplements.

Complementary medicine refers to use of a non-mainstream approach together with conventional medicine. *Integrative medicine* is defined as integrating nontraditional approaches into conventional medicine.² Other terms used to describe CIM include *folkloric, holistic, irregular, nonconventional, non-Western, traditional, unorthodox, and unproven medicine*. Common CIM therapies and health systems include homeopathy, naturopathy, traditional Chinese medicine, acupuncture, chiropractic care, Ayurveda, and massage. This chapter presents a brief overview of common types of CIM other than natural products, which are discussed in [Chapter 51](#).

Overview of Common CIM Health Systems

Major Categories

In the United States, the National Center for Complementary and Integrative Health (NCCIH) classifies CIM therapies into three broad categories.² These include natural products, mind–body practices, and other complementary health approaches. Natural products include herbal medicines, or botanicals; nonbotanicals; minerals; vitamins; and other products such as probiotics. The mind–body practices are diverse and feature procedures or techniques that are taught or conducted by a trained practitioner or teacher. Examples of mind–body medicine include chiropractic manipulation, acupuncture, guided imagery, hypnotherapy, *qi gong*, *tai chi*, yoga, and massage therapy, among many others. The third category is especially broad; it includes traditional healers, energy therapies such as Reiki, and whole medical systems such as Ayurveda, Traditional Chinese Medicine (TCM), homeopathy, functional medicine, and naturopathy.² The NCCIH website (<https://nccih.nih.gov>)

contains extensive information on many forms of CIM.

Healing systems encompass complete sets of theories and practices. A system focuses on a philosophy or lifestyle, such as the power of nature or the presence of energy in the body. Some CIM therapies have been integrated into conventional medicine. Many prescription drugs originally came from natural products such as paclitaxel from the bark of the yew tree, yohimbine from yohimbe bark, and oseltamivir from Chinese star anise. Other examples include etoposide and teniposide derived from *Podophyllum peltatum*, and vincristine and vinblastine derived from *Catharanthus roseus*.⁴

Potential Risks and Benefits

CIM often is considered a form of preventive medicine and is used widely to maintain health and reduce disease risk.² The attraction of CIM includes the potential to treat diseases for which conventional therapies have been ineffective. CIM also may provide an increased sense of patient empowerment and participation. A widespread belief about CIM is that it represents safe and natural therapeutic approaches. Cancer patients have cited the media as influencing their decisions to try these therapies. In addition, some patients use CIM techniques, such as meditation and prayer, to cope with chronic or untreatable illnesses.³

Although some CIM therapies are supported by basic science and clinical evidence, others have not undergone rigorous testing. For example, natural products potentially may cause adverse effects or have clinically significant interactions with prescription and nonprescription drugs, foods, or other supplements. Therefore, CIM therapies should be used under the guidance of a health care provider and not in place of proven conventional therapies.

Research Perspective

In 1992, the U.S. Congress established the Office of Alternative Medicine within the National Institutes of Health (NIH) and provided a budget of \$2 million for rigorous evaluation of CIM practices. In 1998, with the creation of NCCIH, Congress elevated the status of the Office of Alternative Medicine to an NIH center with a budget of \$50 million for fiscal year 1999. The federal appropriations for NCCIH reached \$146.5 million for fiscal year 2019. The mission of NCCIH is to “define, through rigorous scientific investigation, the

usefulness and safety of complementary and integrative health interventions and their roles in improving health and health care.”⁵

In October 1998, the National Cancer Institute (NCI) established the Office of Cancer Complementary and Alternative Medicine (OCCAM), which is housed in the Division of Cancer Treatment and Diagnosis. OCCAM’s mandate is to coordinate and enhance the activities of NCI and to increase the amount of high-quality cancer research and information on the use of CIM. According to OCCAM, in fiscal year 2010, NCI supported \$105,341,737 in CIM-related research. This represents more than 382 projects in the form of grants, cooperative agreements, supplements, or contracts. Other NIH institutes also contribute funds to CIM research, with estimates of almost \$25 billion for all institutes and centers combined.¹

Despite this investment, evidence of the safety and efficacy of CIM may be difficult to obtain. This challenge may be partly related to the fact that many CIM studies are reported in foreign languages and in journals that are not peer reviewed. To conduct evidence-based assessments on CIM, authors of systematic reviews and meta-analyses often broaden literature searches to include languages other than English. Several databases may be searched in addition to PubMed, Embase, Cochrane Library, and MEDLINE. Researchers also may use guides and validated scales, such as the Jadad scale, which has been used to rate the quality of the available studies concerning CIM therapies.⁶

Another issue in evaluating CIM research is the lack of standardization. Many individual therapies involve multiple techniques or dosages, making comparisons difficult. Some types of CIM, such as Ayurveda, do not require providers to be licensed or formally trained, which may contribute to the variable research results.

Experimental design is the most problematic issue in CIM research. The metaphysical aspects of some CIM therapies, such as the harmony between the body and the universe in Ayurveda, are difficult to test with scientific methods.⁷ Integral elements of clinical research, such as placebo control and double blinding, are difficult to conduct in many CIM studies. For example, the participatory nature of meditation prevents blinding of the subject to the active treatment.⁸ Double blinding is a central problem with modalities such as acupuncture, because this therapy cannot be easily delivered by a provider blinded to the intervention. However, this problem can be solved by having a

blinded examiner collect and evaluate outcomes. The Jadad score is sometimes modified for application to acupuncture studies because of the difficulty in blinding the acupuncturist.⁹ In such cases, modified Jadad scoring may include awarding one point if the trial is single blinded or if outcomes are assessed by a blinded investigator rather than the acupuncturist.

To meet the challenge of developing a placebo-controlled study for CIM therapies such as acupuncture, researchers have developed sham treatments to approximate subject blinding. For acupuncture, sham treatment typically involves placement of needles at non-active sites or at a specific distance, usually about 1 inch, from the active sites in the study, whereas depth and stimulation remain the same. Other sham acupuncture techniques involve treatment at actual acupuncture points but without needle penetration. Critics of this approach argue that even pressure at acupuncture points may elicit effects. Although some studies have demonstrated that sham procedures achieved blinding of subjects, methods used to create sham acupuncture vary widely. Sham acupuncture often is not regarded as a true placebo, because the patient is subjected to physical stimulation, and studies have shown that this technique also elicits effects.¹⁰

Working With CIM Providers

Ideally, conventional and CIM providers should work collaboratively for the benefit of the patient. Pharmacists and other health care providers should have an objective attitude toward CIM providers, especially given that some interventions are now provided in conventional medical centers. An example of an integrative approach is a clinic that includes both conventional and CIM providers. Conventional providers may refer patients to CIM practitioners to meet the high demand.

Individuals who use CIM may lack a clear understanding about the therapies. A survey among users of homeopathy in England showed that around 10% of users were confused about what constitutes a homeopathic product.¹¹ Patients should feel comfortable discussing potential CIM therapies with their conventional health care providers, and an increasing number of these providers now integrate certain evidence-based CIM techniques into their practices. Unfortunately, many health care providers lack the resources, knowledge, and training to respond to patients' CIM inquiries. In the following sections, some of the most common complementary and integrative health

systems will be reviewed.

Homeopathy

Homeopathy is a distinct system of medicine with its own pharmacopeia and principles of practice. The term *homeopathy* comes from the two Greek words *homoios* (similar) and *pathos* (suffering or disease). Dr. Samuel Hahnemann developed homeopathy in the early 1800s and coined the term *allopathy* as a synonym for conventional medicine. Homeopathy is based on the principle of “like cures like” or the “law of similars.” This principle maintains that if a substance produces the symptoms of an illness in large doses, that same substance can cure it in very small doses. The more dilute a homeopathic medicine is, the greater its potency. The efficacy of homeopathic medicines is believed to depend not only on the dilution factor but also on vigorous shaking, or *succussion*, which is performed with each dilution.

The homeopathic principle of “like cures like” is often compared with *vaccination*, which involves administration of antigenic material to induce immunity to infectious agents. However, this comparison is not entirely accurate. Vaccines typically contain measurable levels of attenuated or killed pathogens (or their purified antigens) and are used for prophylaxis. In contrast, homeopathic preparations are often so dilute that they contain statistically negligible amounts of the purported active ingredients. In addition, homeopathic remedies generally are used to treat an existing illness rather than for prophylaxis. One exception is *Oscillococcinum*, a homeopathic preparation derived from duck heart and liver, which is used both to prevent and to treat influenza, although evidence of its efficacy is lacking.¹²

Although homeopathic medicines generally are intended to be ingested, they are not classified as dietary supplements. The Food and Drug Administration (FDA) regulates homeopathic medicines under sections 201(g) and 201(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) as drugs recognized in the official *United States Pharmacopeia* (USP), *Homoeopathic Pharmacopoeia of the United States* (HPUS), or *National Formulary* (NF). For homeopathic drugs, the premarket approval process is distinct from the approval process for conventional drugs. Homeopathic drugs are approved with the publication of a monograph by the Homeopathic Pharmacopoeia Convention of the United States (HPCUS) in HPUS. For a homeopathic drug to be included in HPUS, it

must be manufactured according to approved methods of preparation and determined by HPCUS to be safe and effective. The safety and the efficacy of a homeopathic drug are determined by procedures called “provings” (or “research procedures” in the HPUS), which determine the dosages necessary to induce symptoms in healthy individuals. Evidence from homeopathic provings is subject to verification by foundations for the clinical practice of homeopathy; however, according to FDA, “compliance with requirements of the HPUS, USP, or NF does not establish that it has been shown by appropriate means to be safe, effective, and not misbranded for its intended use.”¹³

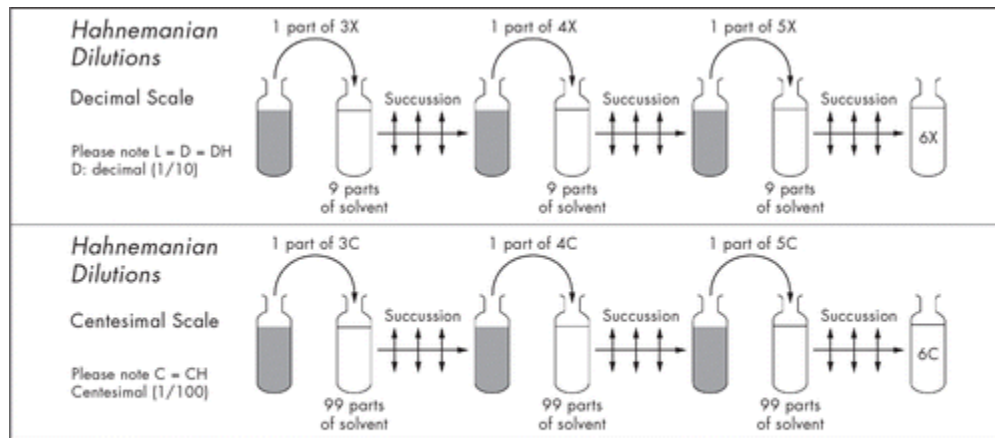
As with conventional drugs, homeopathic remedies may be sold without a prescription if they are intended to treat self-limiting conditions such as headaches and colds. Most homeopathic remedies are available without a prescription, with only about 5% requiring prescriptions from medical care providers. Homeopathic medicines commonly are found in integrative pharmacies that stock dietary supplements and complementary remedies along with standard drugs. Chain pharmacies and health food markets also may carry homeopathic medicines, including pediatric and veterinary formulations.¹³

Homeopathic product sales steadily increased by 16% between 2008 and 2013, with Americans spending \$6.4 billion on these products in 2012.¹⁴ Despite the widespread use of homeopathic products, particularly in children, surveys have demonstrated that confusion exists about what constitutes a homeopathic product, suggesting better patient education is needed.¹¹

Practice

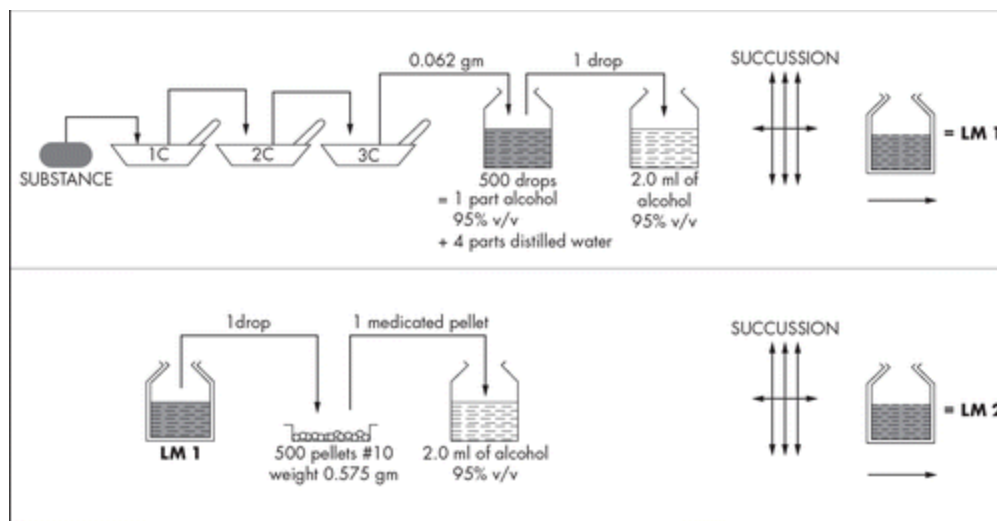
Medicines used in homeopathy are derived from many substances, including botanical, mineral, pharmaceutical, and zoological sources. These substances are serially diluted and succussed (or *trituated*), which is thought to increase the strength or potency of the medication. This process is called “attenuation” or “potentization.” After each attenuation step, the preparation is given a higher number, so a substance that was attenuated 4 times would be designated as 4X, 4C, or LM4 depending on the dilution factor.¹⁵ The decimal (1:10 dilutions) and centesimal (1:100 dilutions) scales of attenuation are used to make X and C potencies, respectively (Figure 52–1). The letter M means 1000C, not the use of 1:1000 dilutions in the attenuation process. A 1:50,000 dilution is represented by the potency LM, which is derived by combining Roman

numerals L and M for 50 and 1000, respectively (although the actual Roman numeral LM means 1000 minus 50, or 950). The method for preparing LM potencies is illustrated in [Figure 52–2](#). Although many homeopathic medicines are derived from highly toxic materials such as aconite and arnica, the final preparations often are so dilute that they are well below toxic dosages.



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FIGURE 52–1 Method for making homeopathic X and C potencies. Decimal scale, designated by an X or D, involves dilutions of 1:10 for each attenuation (dilution with succussion) step taken to make the desired X potency. Centesimal scale, designated by C, involves dilutions of 1:100 for each attenuation step taken to make the desired C potency. (Source: Reprinted with permission from *Introduction to Homeopathic Medicines for Pharmacists*. Newtown Square, PA: Boiron Institute; 2001:9.)



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FIGURE 52–2 Method for making homeopathic LM potencies. The 50-Millesimal scale, designated by LM or Q, involves a complex attenuation process using incremental dilutions of 1:50,000 with succussion. (Source: Reprinted with permission from *The Homeopathic Pharmacopoeia of the United States*. Southeastern, PA: The Homeopathic Pharmacopoeia Convention of the United States Revision Service; December 2004:40.)

Training

More than 30 schools in North America offer training in homeopathy. The Accreditation Commission for Homeopathic Education in North America (ACHENA, formerly Council on Homeopathy Education [CHE]) continually develops professional standards for homeopathic education. Currently, the site lists four accredited homeopathic schools and three schools that are seeking accreditation. The Council for Homeopathic Certification offers a Certificate in Classical Homeopathy (CCH) and provides listings of certified homeopathic practitioners on their website for use by health care providers to identify qualified homeopaths.

Certification with CCH is not recognized by any state as a license to practice homeopathy. Arizona, Connecticut, and Nevada require that homeopaths also be licensed allopathic or osteopathic health care providers. Health freedom acts in some states, such as State of California Senate Bill 577, protect the rights of professionals without medical licenses to practice homeopathy and other modalities that the state deems harmless. Most other states lack specific

regulatory language for homeopathy; therefore, homeopathy falls under the statutes regulating the practice of medicine.

Theory and Evidence

Because homeopathic preparations contain little-to-no active ingredient, critics argue that any demonstrated efficacy is simply a placebo effect. Proponents of homeopathy state that trials have demonstrated effectiveness in either infants or animals, and that these subjects are unlikely to have preconceived expectations that may influence their perceptions. Overall, the effectiveness of homeopathy has not been demonstrated consistently in randomized controlled trials. A 2010 analysis of six reviews in the Cochrane Database of Systematic Reviews concluded that the evidence suggests the effects of homeopathic therapies are similar to those of placebo.¹⁶ A 2014 systematic review and meta-analysis of placebo-controlled randomized controlled trials of individualized homeopathic therapies concluded that the overall quality of the scientific evidence that support homeopathic therapies as being distinguishable from placebo effect are low or unclear, preventing firm conclusions.¹⁷ Citing the contradictory results of clinical trials and the overall lack of evidence determined by systematic reviews and meta-analyses, NCCIH has stated that homeopathy has not been proven definitively to treat any clinical condition. Similarly, the American Medical Association and the American Academy of Pediatrics have neither accepted nor rejected homeopathy in the treatment of any medical condition.¹⁶

Safety

For most homeopathic medicines, the risk of toxicity is low because of the extremely dilute nature of the homeopathic remedies. Studies have suggested that adverse effects are less frequent in patients receiving homeopathic treatments than in those receiving conventional care.¹⁸ The popular cold remedy Zicam has been labeled homeopathic, but some formulations contain significant levels of zinc. The nasal spray formulation containing zinc gluconate is known to cause irreversible damage to human nasal tissue.¹⁹ According to FDA, more than 100 reports of loss of sense of smell have been associated with the use of this product, and this dosage form has since been withdrawn from the U.S. market. Homeopathic remedies are regulated as drugs under the FDCA. FDA currently requires that nonprescription homeopathy drugs and non-homeopathic drugs have similar efficacy and

safety claims, in both advertising and labeling of the products.²⁰ FDA enforcement policies for homeopathic drugs are described in the agency's compliance policy guide *Conditions Under Which Homeopathic Drugs May be Marketed* (CPG 7132.15).²¹ According to a National Health and Medical Research Council study, patients who use only homeopathic products may put their health at risk if they reject, exclude, or delay treatments that have scientifically proven safety and efficacy.¹⁴

Naturopathy

The term *naturopathy* was coined in the late 1890s by German priest Sebastian Kneipp, who practiced herbal medicine and water therapies. Dr. Benedict Lust, who studied under Kneipp, purportedly purchased the rights to naturopathic medicine from another of Kneipp's students. In 1902, Dr. Lust opened the American School of Naturopathy in New York City. Because he was instrumental in promoting this field of medicine, Dr. Lust is generally credited as the founder of naturopathy.

Traditional naturopathy is a philosophy of life and an approach to living that encourages lifestyles and therapies as close to nature as possible. A system of naturopathic therapy employs natural forces such as light, heat, air, water, and massage. Naturopathy focuses primarily on building health rather than on treating disease. The practice of naturopathic medicine emerges from six underlying principles of healing that distinguish the profession from other medical approaches. These principles are based on observation of the nature of health and disease, and they are reexamined continually in light of scientific analysis. The first principle, "The Healing Power of Nature," is that the body has the inherent ability to maintain and restore health. The second principle "Identify and Treat the Causes" implies that the naturopathic health care provider's aim is to identify and treat the cause, rather than the symptoms, of a disease. The third principle is "First Do No Harm." This principle emphasizes the use of less-toxic natural therapies. The fourth principle "Doctor as Teacher" means that the naturopath educates and encourages patients to take responsibility for their own health. The fifth principle is "Treat the Whole Person": the health care provider treats the whole person, taking into account the physical, spiritual, mental, and social aspects of the individual. The final principle "Prevention" requires the naturopath to assess risk factors and hereditary susceptibility to disease and to make appropriate interventions to

prevent further harm or risk to patients.²²

Practice

In most cases of disease or wellness, nutritional counseling and support are major components of naturopathic treatments. Naturopathic health care providers use dietetics, fasting, and nutritional supplementation in practice. Botanical medicine and homeopathy also may be used.

Naturopathic medicine has its own methods of therapeutic manipulation of the muscles, bones, and spine. Naturopaths use ultrasound, acupuncture, *diathermy* (electrically induced heat), exercise, massage, water, heat, cold, air, and gentle electrical pulses. They also may provide natural childbirth care. They offer prenatal and postnatal care using modern diagnostic techniques. In some states, naturopaths may perform minor outpatient surgeries, such as repair of superficial wounds or removal of foreign bodies or cysts.

Because naturopaths believe that mental attitudes and emotional states may influence or cause physical illnesses, they may incorporate counseling, nutritional balancing, stress management, hypnotherapy, biofeedback, and other therapies to help patients heal on the psychological level.

Naturopaths may prescribe substances that are deemed appropriate by the Naturopathic Formulary Advisory Peer Committee. Listed substances depend on state law and vary among states. Some state-specific regulations, such as the Naturopathic Physician Practice Act Rule of Utah,²³ allow naturopaths to prescribe only medicines listed in the *Naturopathic Physician Formulary*.

Training and Licensure

In North America, six schools offer training for the Doctor of Naturopathic Medicine (ND) degree. These include Bastyr University (San Diego, California, and Seattle, Washington); Boucher Institute of Naturopathic Medicine (Vancouver, British Columbia, Canada); the Canadian College of Naturopathic Medicine (Toronto, Ontario, Canada); National University of Natural Medicine (Portland, Oregon); National University of Health Sciences (Chicago, Illinois); and Southwest College of Naturopathic Medicine (Phoenix, Arizona).

Similar to allopathic medical schools, admission into a naturopathic training

program requires 4 years of undergraduate study that includes premedical coursework. The ND degree consists of 4 years of postgraduate training, which includes about 4500 hours of academic and clinical training. Academic training includes courses such as anatomy, biochemistry, microbiology, and pathology. Clinical training encompasses various alternative modalities, including herbal therapy and homeopathy, in addition to mainstream clinical training such as that in cardiology and nutrition. Naturopathic health care providers are educated in modern methods of diagnostic testing and imaging, including radiology, ultrasound, and other imaging techniques. Some naturopaths may participate in residency programs, including integrative programs that train NDs in conventional medical settings.²⁴

In addition to a standard medical curriculum, a naturopath must study holistic therapies that have a strong emphasis on preventing disease and optimizing wellness. NDs are required to complete training in clinical nutrition, acupuncture, homeopathic medicine, botanical medicine, psychology, and counseling. Before they can practice, naturopathic health care providers must pass board examinations set by the North American Board of Naturopathic Examiners, and most states require NDs to complete continuing education hours to renew their licenses.²⁵

The licensing of naturopathic health care providers varies among states. According to the Association of Accredited Naturopathic Medical Colleges (<https://aanmc.org/careers/licensure>) and the Council on Naturopathic Medical Education (<http://www.cnme.org/faq.html>), the practice of naturopathic medicine is allowed in 17 states (Alaska, Arizona, California, Colorado, Connecticut, Hawaii, Idaho, Kansas, Maine, Minnesota, Montana, New Hampshire, North Dakota, Oregon, Utah, Vermont, Washington) and four provinces (British Columbia, Manitoba, Ontario, Saskatchewan).

Because of naturopathy's popularity, more health care providers trained in conventional medicine or other CIM fields are incorporating naturopathic treatments into their practices. health care providers who hold degrees in osteopathy, chiropractic, acupuncture, dentistry, and veterinary medicine may seek additional training in naturopathy; they sometimes use terms such as *holistic*, *natural*, or *integrative* to promote their practices.

Theory and Evidence

The individual methods used in naturopathic medicine vary in their effectiveness. A proper diet may help prevent heart disease, but this measure is recommended in conventional and naturopathic medicine. However, other forms of naturopathic treatment may not be more effective than conventional medicine. For example, acupuncture may help to reduce pain in some instances, but it is not widely recommended for use in place of standard analgesics for extreme pain or in surgery. On the other hand, some naturopathic treatments may be more effective than conventional therapies. For example, a combination naturopathic treatment consisting of nutrition counseling, relaxation techniques, and vitamin and herbal supplementation was more effective than a standardized psychotherapy intervention for anxiety.²⁶

Safety

The safety of naturopathic remedies depends on the treatment and the condition. Naturopathic methods generally are considered safer alternatives for some conventional drugs or treatments. The safety of other approaches such as fasting or other dietary restrictions depends on the individual. As with all CIM therapies, naturopathic treatments should not be used in place of proven conventional therapies for serious medical conditions.

Traditional Chinese Medicine

Chinese medicine is a broad term encompassing many different modalities and traditions of healing, including herbal medicine and acupuncture.⁴ These therapies share a common root in Chinese philosophy, including Taoism, Confucianism, and Buddhism, and may date back more than 5000 years.

In the 1940s and 1950s, the Chinese government undertook an effort to coalesce diverse forms of Chinese medicine into a unified system to be officially defined as traditional Chinese medicine (TCM). The intent was to integrate traditional providers into an organized health system and to provide care for a large population by using familiar and inexpensive methods.

CM is considered to be a complementary or alternative medicine in most of the Western world; however, in several Asian countries, including China, the term for TCM literally means “central medicine.” TCM and Western medicine frequently are used side by side in modern China. As a result, compared with Western countries, China is relatively advanced in using alternative medicine. The most prominent focus of TCM is the treatment of major illnesses, including cancer and heart disease. According to the World Health Organization, TCM is fully integrated into the Chinese health system and is practiced in 95% of Chinese hospitals.²⁷

Technique

TCM emphasizes herbal medicine. In the United States, herbs usually are given as pills, extracts, capsules, tinctures, or powders, but TCM practitioners usually prepare herbal medicines as decoctions.²⁸ More than 2000 different types of herbs are used in Chinese medicine, with 400 used frequently and 50 considered “fundamental” herbs.²⁹ Some Chinese herbs have received attention in Western medicine for treating serious disorders. For example, the *Monascus purpureus* fungus, found in red yeast rice, is a natural source of lovastatin.³⁰ Artemisinin is an antimalarial drug that was isolated from *Artemisia annua* or sweet wormwood L. by Youyou Tu, who was awarded the Nobel Prize in 2015. In addition to its antimalarial activity against *Plasmodium falciparum*, artemisinin has shown potent anticancer activity in vitro.³¹ Bevirimat, derived from the Chinese herb *Syzygium claviflorum*, is being investigated in clinical trials in human immunodeficiency virus (HIV).³⁰

TCM incorporates not only herbs but also minerals, metals, and animal products into therapeutic preparations. The use of animal products has become more infrequent in recent years, in part because of restrictions on certain species, particularly endangered species.

Acupuncture also is considered a form of TCM, although it is regarded as more of a supportive treatment to herbal therapy. Many varieties of acupuncture exist both in Chinese and Western medicine. Classic acupuncture, also known as five-element acupuncture, uses a different needling technique and relies on acupuncture without the use of herbs. Needles used in Japanese acupuncture are smaller than those of other forms of acupuncture. Medical acupuncture refers to an acupuncture therapy that uses knowledge of pathology, anatomy, and physiology but omits certain components of TCM.⁹ Auricular acupuncture

treats the entire body through acupuncture points in the ears only, and electroacupuncture uses electrical currents attached to acupuncture needles. As with many forms of TCM, acupuncture may require multiple treatments and long-term follow-up for symptom improvement and health maintenance.

Cupping and moxibustion are commonly used to complement acupuncture, but these techniques also may be used independently in TCM. They share the principle of using heat to stimulate circulation to break up congestion or stagnation of blood and *chi* (or *qi*), which is the life force central to health and well-being in TCM. Cupping has some relation to the massage technique *tuina*, which uses rapid skin pinching at points on the back to break up congestion and stimulate circulation. Cupping also may be used over acupuncture points or other areas of the body. Popular in the United States, moxibustion involves the burning of dried moxa (mugwort), either on or near the skin, and sometimes in conjunction with cupping or acupuncture on specific points.³²

TCM providers may use other modalities such as meditation and martial arts. *Tai chi chuan* (or *tai chi*) is a meditative form of martial arts that incorporates the theories of *yin* and *yang* from both Taoism and Confucianism. *Tai chi* is practiced to improve balance, coordination, and relaxation, and overall well-being. TCM also may incorporate *feng shui*, which is the art of arranging furniture and objects to increase health and prosperity.

Training

The Accreditation Commission of Acupuncture and Oriental Medicine (ACAOM) accredits professional acupuncture programs and is recognized by the U.S. Department of Education. According to the ACAOM, acupuncture and Oriental medicine is a 3- or 4-year master's degree program, offered by over 70 accredited or candidate colleges in the United States.³³

The National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM) offers four independent certification programs, including Acupuncture, Chinese Herbology, Oriental Medicine, and Asian Bodywork Therapy.³⁴ Acupuncturists who pass national examinations administered by NCCAOM are entitled to identify themselves as board certified in their discipline and as diplomates of the NCCAOM. Licenses to practice acupuncture are granted by individual states. Although requirements vary, many states require acupuncturists to pass the NCCAOM examinations and obtain

continuing education.³⁴

Theory and Evidence

Taoism, Confucianism, and Buddhism provided the basis for the development of Chinese medical theory. According to these philosophies, nature and the laws that govern the ongoing, harmonious flow of life energy through the natural world also govern the body and health. The person is viewed as an ecosystem that is embedded in the larger ecosystem of nature and is therefore subject to the same laws. The life force called *chi* (*qi*) circulates through the body and enlivens it. Health is a function of a balanced, harmonious flow of *chi*, and illness results when there is a blockage or an imbalance in the flow of *chi*. *Yin* and *yang* are opposite and complementary qualities of life energy (*chi*). *Yin* is regarded as the feminine principle and *yang*, the masculine principle. The human being has a system of pathways called “meridians,” sometimes referred to as “channels,” through which *chi* flows. Meridians correspond with specific organs or organ systems (organ networks). Health is believed to be an ongoing process of maintaining balance and harmony of the circulation of *chi* through all the organs and systems of the body. In TCM theory, the body has five organ networks, each corresponding with a particular element.³⁵

Despite the popularity of TCM in the West, its effectiveness remains debatable. Scientific evidence supports the use of acupuncture for several indications including osteoarthritis and various types of pain and nausea. The American Cancer Society states “clinical studies have found that acupuncture may help treat nausea caused by chemotherapy drugs and surgical anesthesia.”³⁶

Moxibustion, which is traditionally used to turn breech babies, has been used with some success, although systematic reviews and meta-analyses have yielded insufficient evidence to support its efficacy.³² In general, few well-designed trials of TCM herbal formulas have been conducted, highlighting the need to improve the methodological quality of TCM research. A 2013 study evaluated systematic reviews of TCM techniques used for a variety of conditions. Forty-one of 70 systematic reviews were unable to conclude if a technique worked for the condition under investigation because of a lack of good-quality evidence.³⁵ Of the 41 systematic reviews, 19 analyzed studies of acupuncture and 22 evaluated studies of Chinese herbal medicine. Potential benefits were proposed in the other 29 systematic reviews; however, researchers were unable to confirm these benefits because of the limited

number or poor quality of the studies.³⁵

Safety

Chinese herbs have been associated with adverse effects. In April 2004, FDA banned the sale of products containing ephedra or ma huang (*Ephedra sinica*) in response to more than 18,000 adverse event reports.³⁷ The U.S. Poison Control Centers have reported that ephedra-related poisonings declined from 10,326 in 2002 to 180 in 2013, and the number of adverse events resulting in major effects or death declined by 98%.³⁷ Some Chinese herbal products have contained toxins or heavy metals.³⁶ In addition, prescription drugs, such as corticosteroids, have been included in the preparations but not listed as ingredients.³⁸ Patients should purchase Chinese herbs from trustworthy sources and should be aware that Chinese herbs can interact with foods, drugs, and other herbs.

Few complications have been reported from using acupuncture. Use of nonsterile needles and improper delivery of treatment are contributing factors to adverse events associated with acupuncture. Potential serious adverse events include infections, injury to the central nervous system, and punctured organs. FDA regulates acupuncture needles and requires that they be sterile, nontoxic, and labeled for single use by a qualified practitioner.³⁹ Because of theoretical and reported adverse effects, acupuncture should be avoided or used cautiously in individuals with heart disease, seizures, infections, bleeding disorders, or neurologic disorders, or among individuals using antithrombotic drugs. Acupuncture should not be performed on areas that have received radiation therapy and for conditions of unknown medical origin. Caution is advised for its use during pregnancy. Frail older adults or otherwise medically complex patients should use acupuncture with caution. Electroacupuncture should be avoided in patients with severe heart disease or cancer and in patients with pacemakers.³⁹

Cupping commonly leaves a temporary bruising of the skin. Moxibustion also may leave a temporary discoloration on the skin, which may be washed off or will disappear on its own. Historically, some traditional providers of moxibustion have intentionally employed more aggressive use of the technique to an extent that might leave minor scarring, but this aggressive form of practice is not used regularly in the West.

Chiropractic Care

Chiropractic focuses on the relationship between spinal structure and body function mediated by the nervous system. It originated in 1895 with D. D. Palmer, a popular hands-on healer in Davenport, Iowa. The term *chiropractic* combines the Greek words *cheir* (hand) and *praxis* (practice). Palmer's original philosophy described the approach as connecting "man the spiritual" to "man the physical" by eliminating interference to the flow of "Innate Intelligence" through each individual. This innate intelligence, an almost metaphysical phenomenon, was thought to flow through the nervous system.⁴⁰ The utilization rate of chiropractic services has increased in the United States. Some studies have shown that women, patients with chronic pain, and patients with back pain are more likely to seek chiropractic care. Common chiropractic services include spinal manipulation and soft-tissue therapy.

Important distinctions exist between the profession of chiropractic, chiropractic care, and spinal manipulation. A chiropractor delivers chiropractic care that involves a full range of treatments delivered in one or more therapeutic encounters. These treatments include procedures and techniques of assessment and a tailored mix of therapeutic interventions to improve a patient's health status. The term *spinal manipulation* or *spinal adjustment* does not operationally define the profession or chiropractic care, although it is a well-known procedure. Chiropractic care also includes other procedures, such as exercise, dietary advice, ergonomic and lifestyle advice, supplement use, all forms of physical therapy and rehabilitation intervention, and referral to other providers as needed.⁴⁰

Techniques

Patients usually lie face down on a Cox table, which is similar to a massage table with an open space in which to place the face. Depending on the technique used, chiropractic visits may last 15 minutes to 1 hour or more. Chiropractors may see patients up to 3 times a week initially and then less frequently over time. Patients can be diagnosed by different procedures including X-ray, computed tomography, magnetic resonance imaging, electrical current, and ultrasound therapy. Thermography also may be used, followed by treatment with ice packs and heat packs.

More than 100 chiropractic and spinal manipulative adjusting techniques may be employed. Spinal manipulative therapy uses many techniques to apply force to an area of the spine joint. Massage or mobilization of soft tissue is used in techniques such as myofascial trigger point therapy, cross-friction massage, active release therapy, muscle stripping, Rolfing, or other forms of structural integration. Mechanical traction or the use of external resistance on the spine also may be used. The cracking sound typically has been associated with cavitation in the spinal zygapophyseal (the neural arch between the joint processes) joints. The cracking or popping of a joint has not been proven to be essential to a clinically effective manipulation.⁴¹

Training

According to the U.S. Department of Labor, an estimated 33,360 chiropractors were practicing in 2017.⁴² The Council on Chiropractic Education (CCE) accredits programs and institutions offering the Doctor of Chiropractic degree, which currently includes 16 schools in the United States (CCEUS) and two in Canada (CCEC).⁴³ According to the Federation of Chiropractic Licensing Boards, all 50 states have formal statutes that recognize and regulate the practice of chiropractic.

The Doctor of Chiropractic degree requires the completion of didactic coursework and clinical training totaling a minimum of 4200 instructional hours. Clinical training with actual patients typically lasts a minimum of 1 year. Specialty training is available through residency programs, which may require an additional 2–3 years of clinical training. Before they are allowed to practice, doctors of chiropractic must pass national board examinations and become licensed. Chiropractors generally do not prescribe drugs, but those who also are licensed naturopaths or other health care professionals may prescribe remedies according to their respective state regulations.⁴⁴

Theory and Evidence

Designing clinical trials to evaluate the efficacy of chiropractic is difficult, primarily because of the issues in developing an appropriate control. Other major issues include a potentially strong placebo effect and the high rate of spontaneous recovery. In addition, patients often seek chiropractic treatment for conditions with poorly understood pathologies, such as fibromyalgia; available evidence is insufficient to support the use of chiropractic for this

condition.⁴⁵ For low back pain, sufficient evidence from both blinded and nonblinded trials supports the use of spinal manipulation, although the benefits are modest and of uncertain clinical significance.⁴⁶ Chiropractic has been used to treat asthma, colic, ear infection, headache, whiplash, and hypertension, although evidence of its effectiveness is insufficient.

Safety

The safety of chiropractic is controversial. Some systematic reviews show that spinal manipulation is associated with mild to moderate adverse effects. The most common serious adverse effects with spinal manipulation are vertebral artery dissection and stroke (VADS).⁴⁷ Published cases in 2010 review revealed 26 deaths associated with chiropractic spinal manipulation, and more fatalities may be unpublished.⁴⁸ Few studies have shown proper research of chiropractic spinal manipulation and its association with VADS, myelopathy, vertebral disc extrusion, and epidural hematoma.⁴⁸ Patients with VADS may be more likely to seek chiropractic treatment because of the disorder's initial symptoms, which suggests a potential sampling bias. A 2009 systematic review showed that adverse events occurred with a frequency of 33%–60.9%, but serious adverse events were rare, with as few as 1.46 serious adverse events and 2.68 deaths for every 10 million manipulations. Although this study did not support a strong causal relationship between chiropractic manipulation and the adverse events, the authors stated further high-quality studies are needed to assess its safety.⁴⁹

Patients with osteoporosis or any type of acute arthritis should either avoid chiropractic adjustment or use it cautiously because of the risk of fracture. Caution also is warranted in patients with bleeding disorders, migraines, and tumors or metastases to the spine. Patients with symptoms of vertebrobasilar vascular insufficiency, aneurysms, arteritis, or unstable spondylolisthesis should avoid chiropractic care. Patients receiving anticoagulant therapy also should be advised to avoid chiropractic care.

A final consideration is that chiropractors traditionally have been believed to discourage the use of routine vaccinations, although available data have suggested otherwise. Using data from the 2007 National Health Interview Survey, 12,164 adults were identified as individuals who were at high risk for developing influenza. The likelihood of receiving influenza vaccine was similar among individuals who used chiropractic care and those who did not.⁵⁰

Ayurveda

Ayurveda originated in India more than 5000 years ago and is probably the world's oldest system of natural medicine.⁵¹ When translated, *Ayurveda* means science of life, which stems from the spiritual teachings known as the Vedas. Ayurveda may be the original basis for Chinese medicine and is an integrated system of specific theories and techniques that employ diet, herbs, exercise, meditation, yoga, and massage or bodywork. The goal of Ayurveda is to achieve optimal health on physical, psychological, and spiritual levels.

In India, Ayurveda involves the eight principal branches of medicine: pediatrics, gynecology, obstetrics, ophthalmology, geriatrics, otolaryngology, general medicine, and surgery. In Western countries, the practice of Ayurveda is less focused on its spiritual roots than on its use as a form of CIM. Ayurveda relies on the individual's willingness to participate in lifestyle and behavior changes.

Technique

Ayurveda teaches that vital energy (*prana*) is the basis of all life and healing.⁵¹ As *prana* circulates throughout the human body, it is governed by the five elements of earth, air, fire, water, and ether. The five elements combine with one another into pairs called *doshas* that include *vata* (ether and air), *pitta* (fire and water), and *kapha* (earth and water). Health is thought to be a state of balance and harmony among the five elements, and illness occurs when there is an imbalance or lack of harmony among them.

The regulation of diet as a form of therapy is a central idea in Ayurveda. An individual's temperament and mental and spiritual development can be influenced by the quality and quantity of food consumed. An important principle in Ayurveda is that "there is nothing in the world that is not a medicine or food." Foods and herbs are described in terms of their energetic qualities rather than chemical properties. Sweet foods (called *madhura*) provide nourishment and coolness and also aid in increasing body weight. Sour foods (called *amla*) provide warmth and aid weight gain. Salty foods (*lavana*) provide warmth, stimulate the senses, and aid weight gain. In contrast, bitter foods (*katu*) provide coolness and help weight loss. Pungent foods (*tikta*) also aid weight loss but provide warmth and stimulation. Numerous herbs and spices, including turmeric and cumin, are used in

Ayurveda.⁵¹

Ayurveda holds that each 24-hour cycle is divided into 4-hour segments governed by the *doshas*. These time periods are believed to correspond with nature. Ayurvedic providers guide patients to plan their activities to be in harmony with these natural principles of timing.⁵¹

A provider usually interviews the patient about his or her medical history. The provider then palpates the patient's wrist to determine subtle qualities of the pulse. Providers also may evaluate the appearance of the tongue, face, lips, nails, or eyes. Laboratory tests of blood, urine, and stools may be used to help with the diagnosis. The initial consultation usually is the longest, lasting from 45 to 90 minutes or longer. Follow-up consultations may be spaced by several weeks or months to monitor the individual's progress. Follow-up usually will entail brief office visits that involve a diagnostic review and an adjustment of the regimen.

Training

In India, 240 institutions offer graduate level degrees in Ayurvedic medicine; the standard length of training is at least 5 years. Despite the abundance of institutions, the standard of Ayurvedic education in India is poorly structured and largely unregulated, which has resulted in a global negative perception of the practice.⁵²

According to NCCIH, no national standard for Ayurvedic training or certification exists in the United States. Ayurveda is practiced in Western medicine by health care providers who are licensed in a variety of disciplines.⁵¹ Allopathic and osteopathic health care providers, naturopaths, acupuncturists, primary care providers, massage therapists, and chiropractors may practice Ayurveda. Health counselors, educators, or consultants also may incorporate Ayurveda into their practices without specific licensing. In Western countries, two major approaches to training and practice exist. The first is offered by diverse teachers and providers, many of whom are either from India or were trained there. The second consists of devotees of Maharishi Mahesh Yogi, the Indian spiritual teacher who introduced Transcendental Meditation (TM) to the West. In 1980, this group coined the term *Maharishi Ayur-Ved*, a practice that incorporates TM as part of an Ayurvedic approach.

Theory and Evidence

Some of the more metaphysical aspects of Ayurveda, such as harmony between the body and the universe, are difficult to assess with modern scientific methods.⁷ Several herbal formulations have been studied in Western-style clinical trials, but current evidence is inadequate to recommend Ayurveda for any indication.

Safety

Many different Ayurvedic herbs exist, and they are frequently taken in combination with other herbs and/or minerals. Safety and toxicity will vary depending on the herb and its preparation. In general, Ayurvedic herbal medicines should be used cautiously, because their potencies may not be tested or standardized. Therapeutic levels of sildenafil have been detected in Ayurvedic herbal preparations used for aphrodisiac purposes.⁵³ Patients should purchase Ayurvedic herbs from trustworthy sources and should be aware that Ayurvedic herbs can interact with other herbs, foods, and drugs. For example, ginger, which is commonly used in Ayurveda, may increase the risk of bleeding when used with antithrombotic drugs.

Heavy metal contamination continues to be a concern in Ayurvedic medicines. In addition to herbs, Ayurvedic formulas known as *rasa shastra* also may contain metals such as arsenic, mercury, and zinc. Providers claim that these medicines are safe when properly prepared and administered. However, toxicity with these products have been documented in case reports. According to the U.S. Centers for Disease Control and Prevention, 12 cases of lead poisoning in five states were associated with Ayurvedic medicines from 2000 to 2003.⁵⁴ Consequently, patients are advised to use Ayurvedic herbs cautiously. Products that have USP seals of quality approval have been tested and should not contain unacceptable levels of harmful metals. Product testing information also is available from sites such as [ConsumerLab.com](https://www.ConsumerLab.com) (see [Chapter 50](#)).

Massage

Soft tissue manipulation has been practiced for thousands of years in diverse

cultures. Chinese use of massage dates to 1600 BC, and as early as 400 BC, Hippocrates referred to the importance of primary care providers being experienced with “rubbing.”

Massage spread throughout Europe during the Renaissance and was introduced in the United States in the 1850s. By the early 1930s, massage became a less prominent part of Western medicine. Renewed interest in therapeutic massage emerged in the 1970s, particularly among athletes to promote well-being, relaxation, analgesia, stress relief, healing of musculoskeletal injuries, sleep enhancement, and quality of life. Massage is one of the most common forms of CIM therapy used in the United States.

A common goal of massage therapy is to help the body heal itself. Touch is fundamental to massage therapy and is used by therapists to locate painful or tense areas, to determine how much pressure to apply, and to establish a therapeutic relationship with patients.

Technique

Different therapeutic techniques can be classified as massage therapy. Most involve the application of fixed or moving pressure or the manipulation of the patients’ muscles and connective tissues. Providers may use their hands or other areas such as forearms, elbows, or feet. Lubricants may be used to aid the smoothness of massage strokes. Examples of massage therapy include Swedish massage, sports massage, deep tissue massage, and trigger point massage.

Training

Training requirements for massage therapy vary in the United States, but they generally involve 500–1000 hours for certification by the National Certification Board for Therapeutic Massage and Bodywork. More than 1000 massage training programs exist, and some have received accreditation by the Commission on Massage Therapy Accreditation, which is recognized by the U.S. Department of Education. Upon fulfilling the necessary requirements, massage therapists receive the designation of Nationally Certified in Therapeutic Massage and Bodywork. A national examination is available from the National Certification Board for Therapeutic Massage and Bodywork. Most states require massage therapists to be certified before practicing.

Theory and Evidence

Research on massage therapy is limited, and available studies frequently used a variety of techniques and trial designs. Although studies have identified potential benefits in some conditions, most studies are of lower quality because of the low number of participants or poor design. In people with knee osteoarthritis, short-term massage has shown statistically and clinically significant improvement in symptoms.⁵⁵ Massage remains popular for improving relaxation, mood, and overall well-being, particularly in palliative care.

Safety

Adverse effects have been reported with massage. For example, fractures, discomfort, bruising, swelling of massaged tissues, and liver hematoma have been reported. Vigorous massage should be avoided in patients with bleeding disorders, peripheral vascular disease, or thrombocytopenia, or in those receiving antithrombotic therapy. According to preliminary data, blood pressure may increase in healthy patients following vigorous massage (e.g., trigger point therapy, which focuses on painful muscle knots). However, in patients with hypertension, massage may lower blood pressure. Areas that should not be massaged include those with osteoporotic and other fractures, open or healing skin wounds, skin infections, and blood clots, and those that have undergone surgery. Massage and other touch-based therapies should be used cautiously in patients with a history of physical abuse. Women who are pregnant should consult their obstetrician before beginning massage therapy. Allergies or skin irritation can occur with the oils used in massages, such as olive and mineral oil.

Conclusion

Patients increasingly seek care from CIM providers and health systems. Although some historical and scientific evidence supports the effectiveness of some approaches, it is difficult to make general statements on the safety and efficacy of CIM. Because important components of clinical trials such as placebo controls and blinding are difficult to achieve for some forms of CIM therapy, evidence of effectiveness is limited. Because the use of CIM continues

to increase, both patients and conventional health care providers should be informed about the potential risks and benefits of CIM techniques. [Table 52–1](#) lists common evidence-based uses of CIM health systems. Cases 52–1 and 52–2 provide examples of disorders that are amenable to CIM therapies.

TABLE 52–1 Common Health Issues with Evidence of Benefit from CIM	
Condition	CIM Treatment
Osteoarthritis	Acupuncture
Chronic pain, fibromyalgia, postoperative pain	Acupuncture
Nausea	Acupressure
Low back pain	Chiropractic
Quality of life in cancer patients	Massage
Anxiety and stress	Therapeutic touch

Key: CIM = Complementary and integrative medicine. Source: Reference 4.

More patients are using the internet as a source of health information before they consult a health care provider. As health information has become more available, patients have increased their responsibility for health decisions and should be encouraged to inform their health care provider whether they are using any CIM approaches. Similarly, all Western health care providers, including pharmacists, must be knowledgeable about CIM health systems and the evidence that supports or refutes their use.

Case 52–1

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	

1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	The patient comes to the pharmacy seeking advice to help relieve her constant stress. She works as a sales associate in a large department store. She noticed that her stress and anxiety levels increase when she has to deal with her supervisors. The patient states that her job has been very stressful after a change in administration.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	The patient mentions working additional hours to cover her financial responsibilities. She has been under intense pressure the past few months after her husband lost his job. Her sleep has been affected by her stress; she mentions sleeping only 3-4 hours a night. She also mentions that her stress is relieved when she takes their dog on a walk.
c. Description of the patient's efforts to relieve the symptoms	Patient states that she has tried taking diphenhydramine without relief.
d. Patient's identity	Allison Johns
e. Patient's age, gender, height, and weight	47 years old, female, 5 ft 5 in., 180 lb
f. Patient's occupation	Sales associate
g. Patient's dietary habits	Mostly fast food or frozen foods; she does not have the time to do much cooking lately. Drinks 5-6 cups of coffee a day.
h. Patient's sleep habits	She feels stressed and has difficulty sleeping at night.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Hypertension: treated with lisinopril 10 mg tablet daily
	Occasionally takes melatonin 3 mg tablet at night when she has difficulty sleeping.
j. Allergies	None
k. History of other adverse	None

reactions to medications	
I. Other (describe) _____	n/a
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Stress, insomnia
3. Identify exclusions for self-treatment.	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer the patient to her HCP or to an integrative medicine provider, such as a certified yoga instructor. (2) Advise the patient to consider yoga practices to reduce stress: for example, specific breathing techniques, meditation, and different physical postures. (3) Recommend sleep hygiene practices, including limiting alcohol and caffeine consumption, and establishing a consistent sleep-wake pattern. (4) Recommend self-care until the patient can see an appropriate provider.(5) Take no action.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Recommend yoga with a certified trainer and sleep hygiene best practices. Suggest meditation and relaxation therapy
6. Describe the recommended therapeutic approach to the patient or caregiver.	"Practicing yoga may help to relieve your stress symptoms. Proper sleep hygiene should help your insomnia and stress. Avoid stimulants such as caffeine, and limit alcohol intake. Regular exercise can alleviate stress and promote good sleep. In addition, many programs for meditation are available."

7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	“A naturopath or certified yoga trainer may be able to help you manage the stress as well as improve your sleep through diet and lifestyle changes. Previously you used walking your dog as a stress reliever and occasionally took melatonin. These measures have shown some benefit, but you are still looking for more options. Yoga may help to reduce some of your stress-related symptoms and help regulate your sleep.”
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	“Yoga practices may require training, but they will likely help with your stress and other concerns. The good sleep hygiene practices may help with your symptoms and just require consistent application to see an effect.”
Solicit follow-up questions from the patient or caregiver.	“How long will it take to see the effect?”
Answer the patient’s or caregiver’s questions.	“Responses are variable, so it is important to be consistent in practicing the yoga techniques you learn and in following the sleep hygiene practices.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Call the patient in a week to evaluate the outcome.

Key: HCP = Health care provider; n/a = not applicable.

Case 52–2

Relevant Evaluation Criteria	Scenario/Model Outcome
Collect	

1. Gather essential information about the patient's symptoms and medical history, including	
a. Description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient presents to the pharmacy to buy acetaminophen for pain associated with his osteoarthritis. He recently was diagnosed with mild osteoarthritis and has been controlling his pain somewhat with acetaminophen. The patient mentions searching for other nondrug options that can help ease his pain. He worries that as his disease progresses, he will need to take more medications and wants to ask you about available nondrug treatment options.
b. Description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	The patient has noticed increased stiffness and pain, especially in the morning.
c. Description of the patient's efforts to relieve the symptoms	He is taking acetaminophen with some relief.
d. Patient's identity	Steve Harts
e. Patient's age, gender, height, and weight	68 years old, male, 5 ft 6 in., 220 lb
f. Patient's occupation	Accountant; currently working part time until he retires next year.
g. Patient's dietary habits	He loves preparing home cooked meals for himself and his family. He says that he enjoys eating steak at least twice a week, but he tries to vary his diet the rest of the week.
h. Patient's sleep habits	Sleeps 8–9 hours a night.
i. Concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Hypertension on valsartan 80 mg/day;
	hyperlipidemia on rosuvastatin 10 mg/day

j. Allergies	Takes ACE inhibitors for cough.
k. History of other adverse reactions to medications	None
l. Other (describe) -----	n/a
Assess	
2. Differentiate patient's signs/symptoms, and correctly identify the patient's primary problem(s).	Pain and stiffness
3. Identify exclusions for self-treatment.	None
4. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine whether referral to a health care provider is required, and share this information with the patient or caregiver.	Options include (1) Refer the patient to his HCP. (2) Suggest that he consider yoga practices, tai chi, or massage to control his pain and stiffness. (3) Recommend self-management programs. (4) Refer the patient to a physical therapist to determine the appropriate exercises for him. (5) Suggest using patellar taping or thermal agents after consulting with his HCP.
Plan	
5. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Patient should consult an HCP.
6. Describe the recommended therapeutic	"You should consult your regular health care provider for possible referral to a yoga, acupuncture, tai chi, or massage

approach to the patient or caregiver.	practitioner. Tai chi or acupuncture may be good options. Also consider referral to a physical therapist.”
7. Explain to the patient or caregiver the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	“This option should help you to slow down the progression of the disease and to avoid the need for surgery.”
Implement	
8. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient or caregiver.	Provide an evidence-based patient education handout on yoga, acupuncture, and physical therapy for the patient to examine.
Solicit follow-up questions from the patient or caregiver.	“How can I prevent this condition from getting worse?”
Answer the patient’s or caregiver’s questions.	“Keep a log of activities that exacerbate your condition, and try to avoid them. Explore different integrative therapies to find the one that works best for you. Try patellar taping or thermal agents first. These measures will help you avoid medication-associated adverse events.”
Follow-up: Monitor and Evaluate	
9. Assess patient outcome.	Contact the patient within a few days to ensure that he has sought care.

Key: ACE = Angiotensin-converting enzyme; HCP = health care provider; n/a = not applicable.

Key Points for CIM Health Systems

- The term *complementary and integrative medicine* (CIM) is a broad group of healing philosophies, diagnostic approaches, and therapeutic interventions that, in general, are not considered part of the conventional Western health system. Common CIM approaches include homeopathy, naturopathy, TCM and acupuncture, chiropractic care, Ayurveda, and massage.
- Homeopathy is based on the principle of “like cures like,” which states that if a substance produces the symptoms of an illness in large doses, that same substance can cure it in very minute dosages. The efficacy of homeopathy has not been determined for any clinical condition, although the risk of toxicity is low.
- Naturopathy employs natural forces such as light, heat, air, and water through nutrition, botanical medicine, psychotherapy, acupuncture, homeopathy, massage, and spinal manipulation; this therapy focuses on building health rather than on treating disease. Naturopathy is based on six principles: (1) the healing power of nature, (2) identifying and treating the cause, (3) doing no harm, (4) treating the whole person, (5) the conventional primary care provider as teacher, and (6) preventing disease.
- TCM includes herbal medicines as well as techniques such as acupuncture, exercise, massage, moxibustion, and cupping. TCM focuses on the life force (*chi*), which is thought to circulate through the body through meridians (channels) that connect all major organs. *Chi* consists of *yin* and *yang*, which are opposite and complementary qualities. Illness is believed to result when these forces are unbalanced. An acupuncturist inserts sterilized needles into channels of energy to try to restore balance to the patient’s *chi*.
- Chiropractic focuses on the relationship between spinal structure and body function mediated by the nervous system. Spinal manipulation is a well-known procedure, but chiropractic care also includes other procedures, including all forms of physical therapy and rehabilitation intervention. Spinal manipulation may be helpful for back pain.
- Ayurveda is an integrated system employing diet, herbs, exercise,

meditation, yoga, and massage or bodywork. Ayurveda teaches that vital energy (*prana*) is the basis of all life and healing. As *prana* circulates throughout the body, it is governed by the five elements of earth, air, fire, water, and ether. The five elements combine with one another into pairs called *doshas*, which include *vata* (ether and air), *pitta* (fire and water), and *kapha* (earth and water).

- Touch is fundamental to massage therapy and is used by massage therapists to locate painful or tense areas, to determine how much pressure to apply, and to establish a therapeutic relationship with patients.

Color Plates

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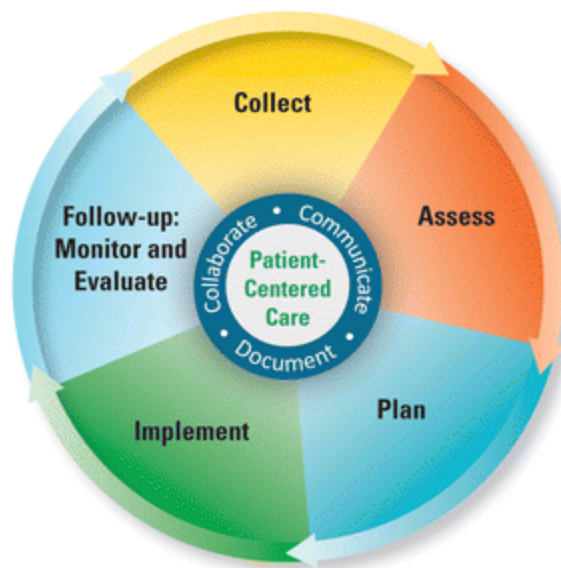
Color Plate-2



1 The seven pillars of self-care illustrate the broad scope of self-care, as defined by the International Self-Care Foundation. (See Chapter 1, Table 1-1, for discussion of the seven elements.) (Adapted with the permission of the International Self-Care Foundation.)

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Pharmacists' Patient Care Process

Pharmacists use a patient-centered approach in collaboration with other providers on the health care team to optimize patient health and medication outcomes.

Using principles of evidence-based practice, pharmacists:

Collect

The pharmacist assures the collection of the necessary subjective and objective information about the patient in order to understand the relevant medical/medication history and clinical status of the patient.

Assess

The pharmacist assesses the information collected and analyzes the clinical effects of the patient's therapy in the context of the patient's overall health goals in order to identify and prioritize problems and achieve optimal care.

Plan

The pharmacist develops an individualized patient-centered care plan, in collaboration with other health care professionals and the patient or caregiver that is evidence-based and cost-effective.

Implement

The pharmacist implements the care plan in collaboration with other health care professionals and the patient or caregiver.

Follow-up: Monitor and Evaluate

The pharmacist monitors and evaluates the effectiveness of the care plan and modifies the plan in collaboration with other health care professionals and the patient or caregiver as needed.



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2 The Pharmacists' Patient Care Process was developed by the Joint Commission of Pharmacy Practitioners to provide a consistent process in the delivery of patient care across the profession (see Chapter 2).

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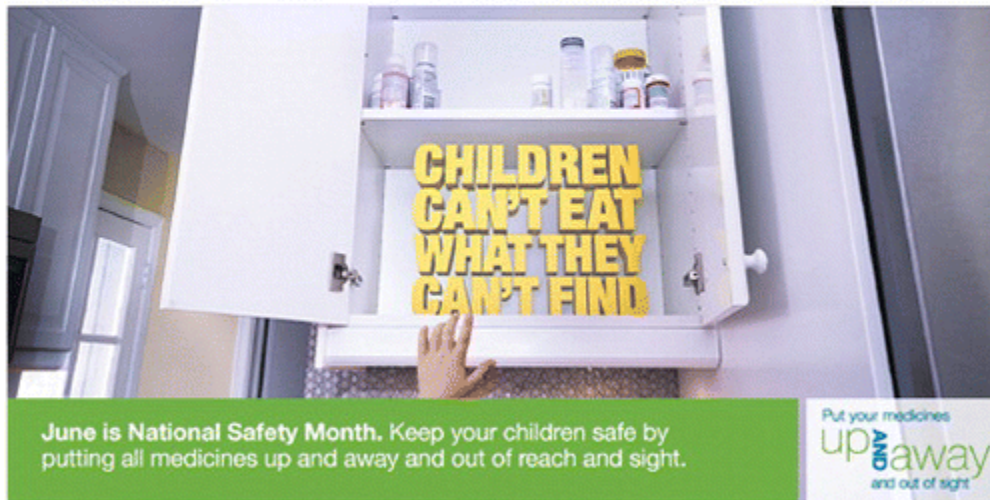
3 Boy Scouts and Venturers ages 11–17 years can earn the SCOUTStrong Be MedWise award after they complete four lessons on safe and responsible nonprescription medication use. The award is sponsored by a partnership

between the National Council on Patient Information and Education (NCPIE) and the Boy Scouts of America (see Chapter 1). (Photograph of badge used with the permission of the Boy Scouts of America.)



Follow

We live for our kids' safety, and it starts at home!
Store all [#MedsUpAway](#) - out of children's reach
and sight [#NSM15](#)



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4 The Up and Away project, a collaborative effort by public health agencies, private sector companies, professional organizations, consumer and patient advocates, and academic experts, has developed strategies to keep children safe from unintentional medication overdoses (see Chapter 1).



1A—Pinworm, adult (courtesy of
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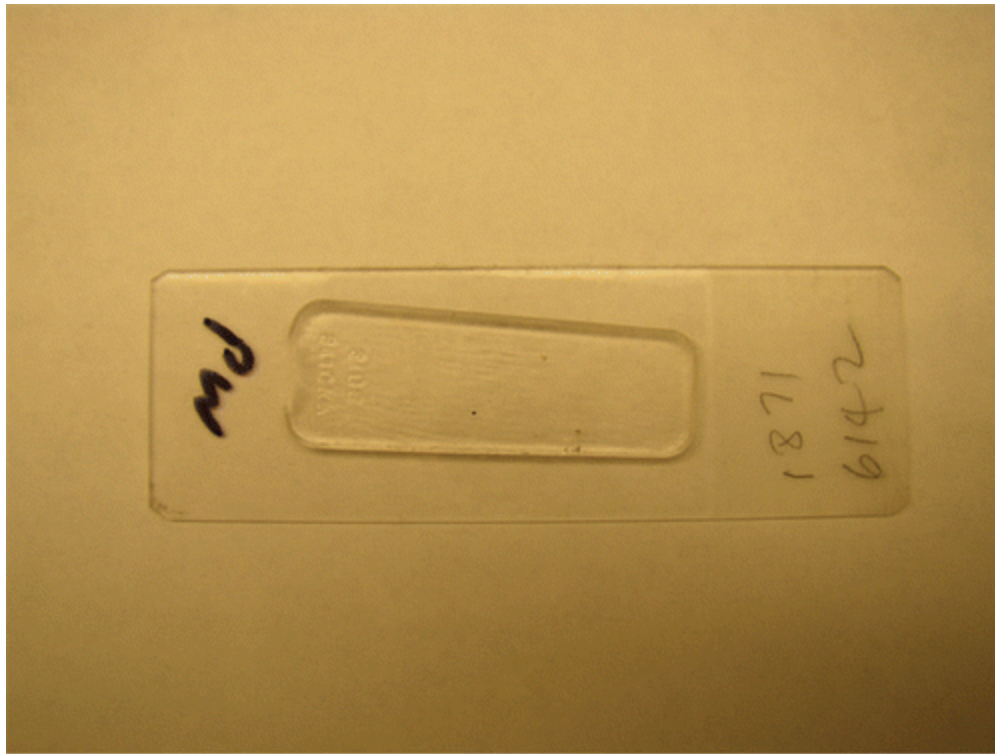
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1B—Pinworm eggs (courtesy of
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1C—Pinworm detection kit (courtesy of Jeffrey A. Goad, PharmD, © 2003)

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5A, B, and C Pinworm infection, the most common worm infestation in the United States, is caused by ingestion of pinworm eggs from fecally contaminated hands, food, clothing, or bedding. A, The adult pinworm is a small (1-cm long), white, thread-like worm with a pin-shaped, pointed tail. B, The mature female stores approximately 11,000 eggs in her body, which she deposits in the perianal region of the host, usually at night. Reinfection occurs when the hatched larvae return to the large intestine or when eggs are transferred from the anus to the mouth and swallowed. C, Commercial pinworm detection kits use a sticky paddle, instead of tape, to affix the adult pinworm to a slide, which is then examined microscopically (see Chapter 18). (Photographs 6A and B courtesy of Lawrence R. Ash, PhD, and Thomas C. Orihel, PhD, © 1997, *Atlas of Human Parasitology*. 4th ed. Chicago: ASCP Press; 1997. Photograph 6C courtesy of Jeffery A. Goad, PharmD, University of Southern California, School of Pharmacy, Los Angeles, © 2003.)

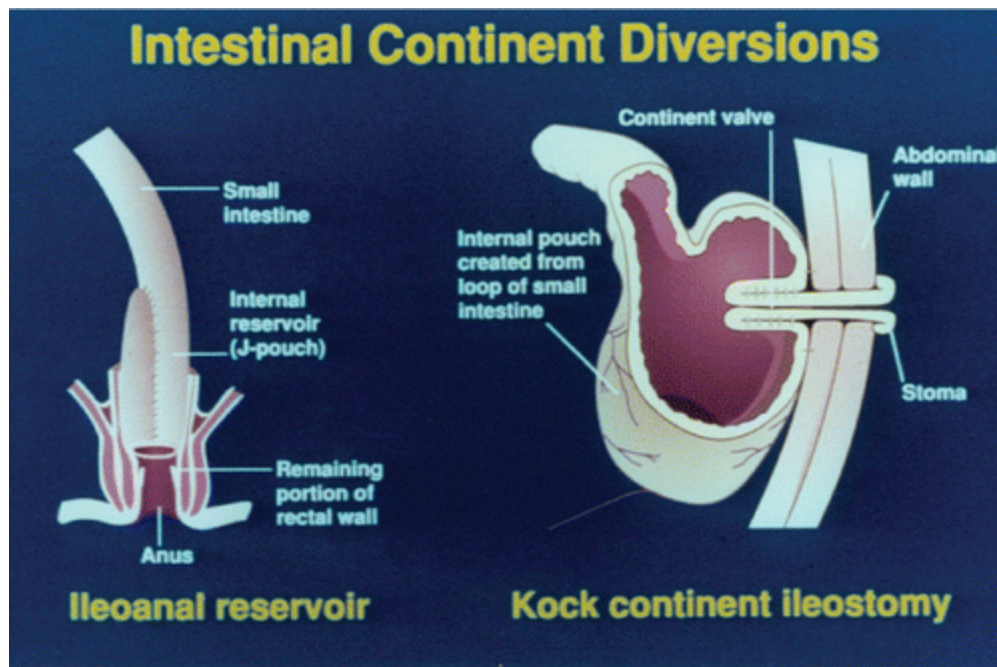
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2A—Ileostomy with stoma (courtesy of Joan Lerner Selekof, BSN, CWOCN, © 2003)

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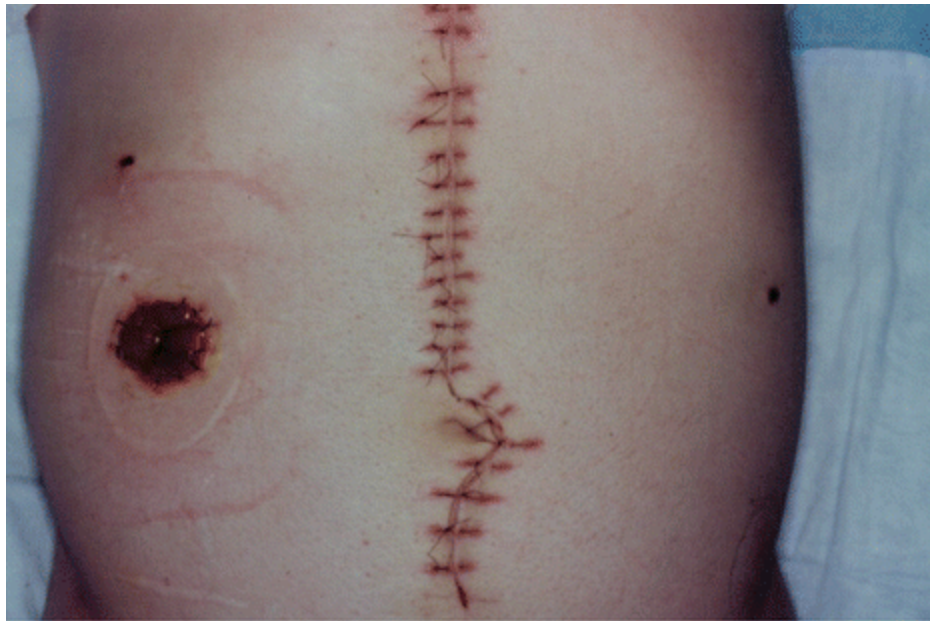


2B–Ileoanal reservoir and Kock continent ileostomy (courtesy of Hollister Inc., © 2003)

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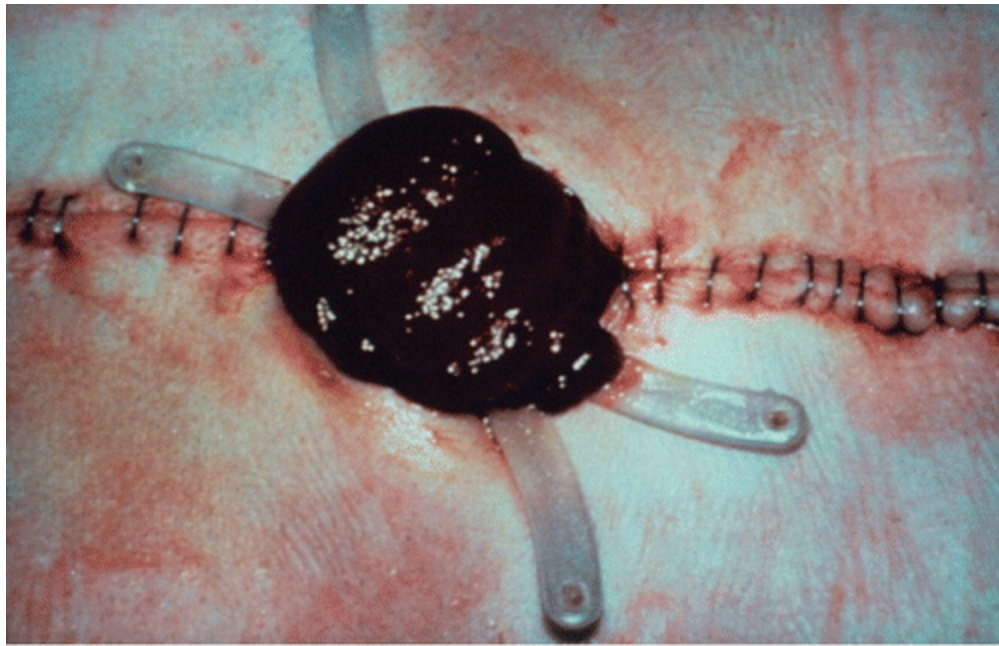
6A–B There are three major types of ostomies: ileostomy, colostomy, or urinary diversion. **A**, In an ileostomy, a portion of the ileum is brought through the abdominal wall. **B**, The two most common types of continent ileostomies are the ileoanal reservoir and the Kock continent ileostomy. The ileoanal reservoir is created by stripping diseased mucosa from the rectum, creating an internal pouch from the ileum, and pulling the distal end of the pouch through the rectum and attaching it. In the Kock continent ileostomy, an internal pouch is created from the ileum and an intussusception of the bowel is used to create a “nipple.”



2C—Colostomy, ascending (courtesy of Joan Lerner Selekof, BSN, CWOCN, © 2003)

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2D–Colostomy, loop (courtesy of Hollister Inc., © 2003)

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2E—Colostomy,
transverse, double-
barrel (courtesy of Joan
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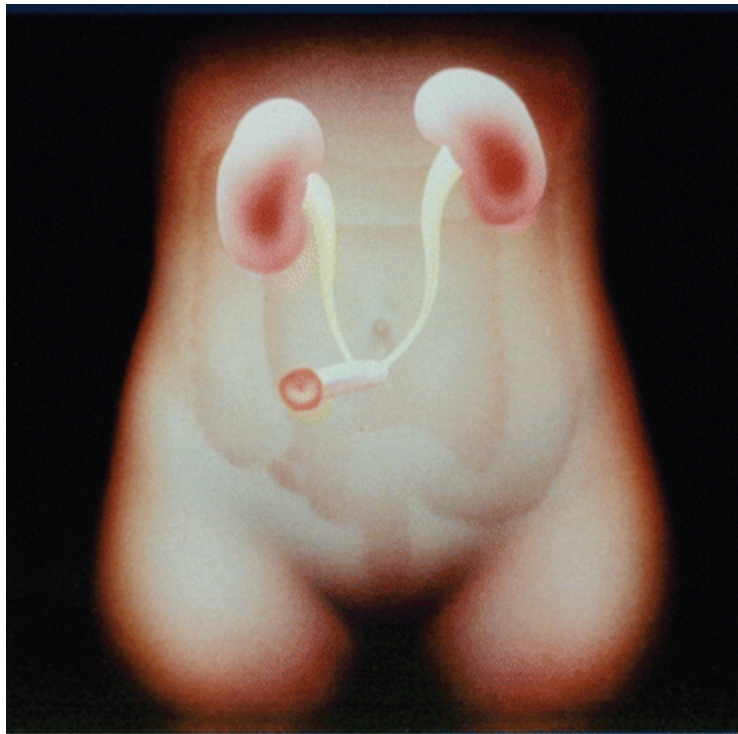
2F—Colostomy, descending (courtesy of Joan Lerner Selekof, BSN, CWOCN, © 2003)

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6C–F Colostomies are located on the ascending, transverse, or descending/sigmoid colon. **C**, Ascending colostomies are uncommon. The ascending colon is retained, but the rest of the large bowel is removed or bypassed. The stoma is usually on the right side of the abdomen. The transverse colon is the site of most temporary colostomies. A loop of the transverse colon is lifted through the abdominal incision, and a rod or bridge is placed under the loop to give it support. **D**, Loop colostomies have one large opening, but two tracts. The proximal tract discharges fecal material; the distal tract secretes small amounts of mucus. **E**, In a double-barrel transverse colostomy, the bowel is completely divided by bringing both the proximal end and the distal end through the abdominal wall and suturing them to the skin. **F**, Descending and sigmoid colostomies are fairly common and generally are on the left side of the abdomen.

Color Plate-5



2G—Ileal conduit (courtesy of Hollister Inc., © 2003)

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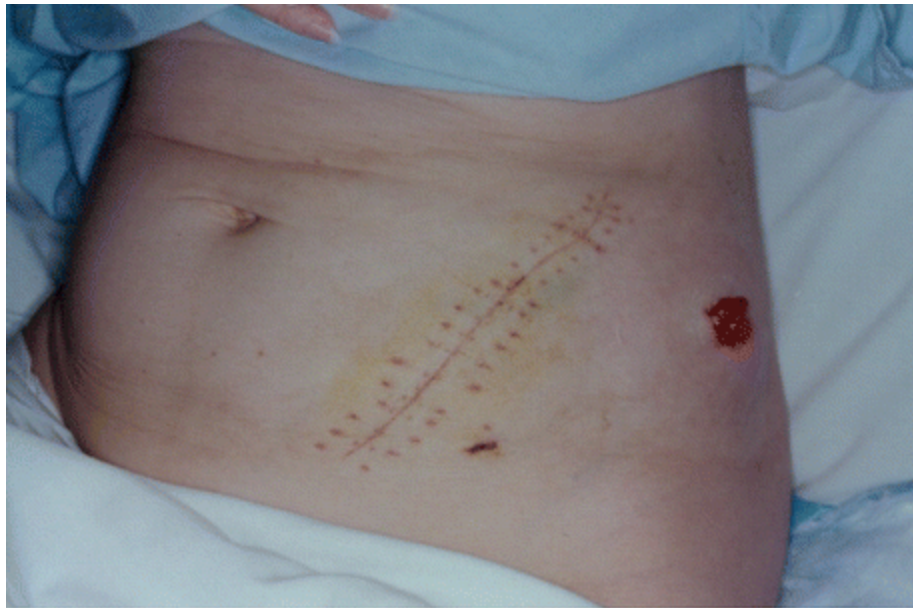
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2H—Ileal conduit with mucous shreds (courtesy of Joan Lerner Selekof, BSN, CWOCN, © 2003)

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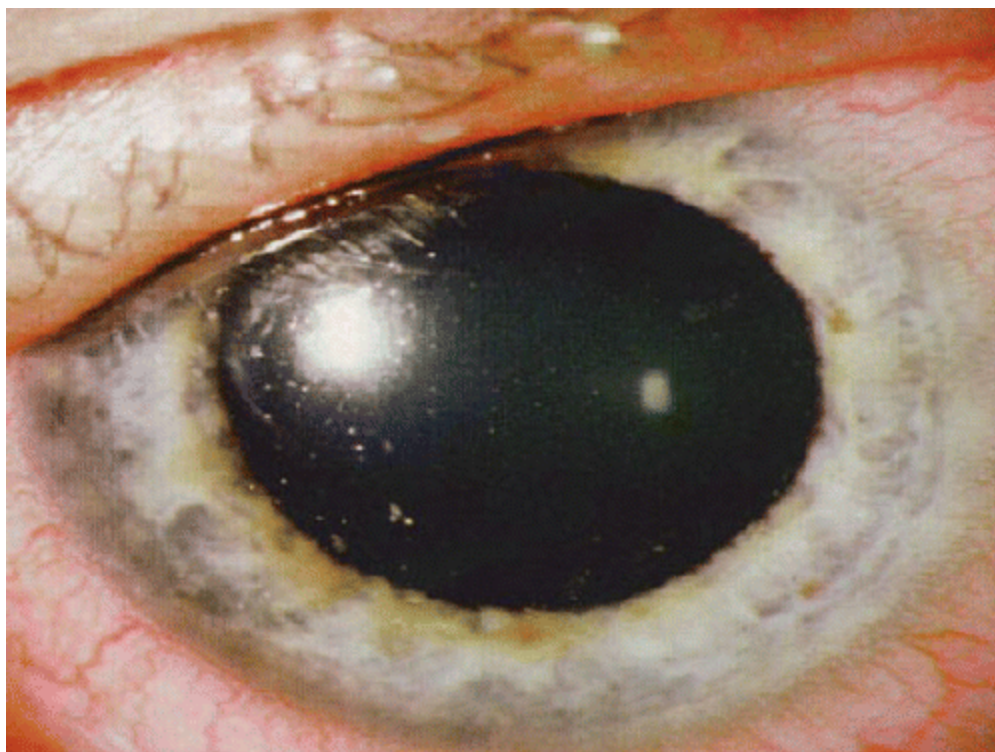


2I—Ureterostomy (courtesy of Joan Lerner Selekof, BSN, CWOCN, © 2003)

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6G–I Urinary diversion surgery diverts the urinary stream through an opening in the abdominal wall. G, In the ileal conduit, the most common type of urinary diversion, ileal and colon conduits are created after removal of the bladder by implanting the ureters into an isolated loop of bowel, the distal end of which is brought to the surface of the abdomen. H, Mucous shreds will be present if the bowel is used to create the diversion. I, In a ureterostomy, one or both ureters are detached from the bladder and brought to the outside of the abdominal wall, where a stoma is created. This procedure is used less frequently because the ureters tend to narrow unless they have been dilated permanently by previous disease (see Chapter 22). (Copyrighted photographs 2B, D, and G courtesy of Hollister Incorporated, Libertyville, Illinois. Copyrighted photographs 2A, C, E, F, H, and I courtesy of Joan Lerner Selekof, BSN, CWOCN, University of Maryland Medical Center, Baltimore, Maryland.)

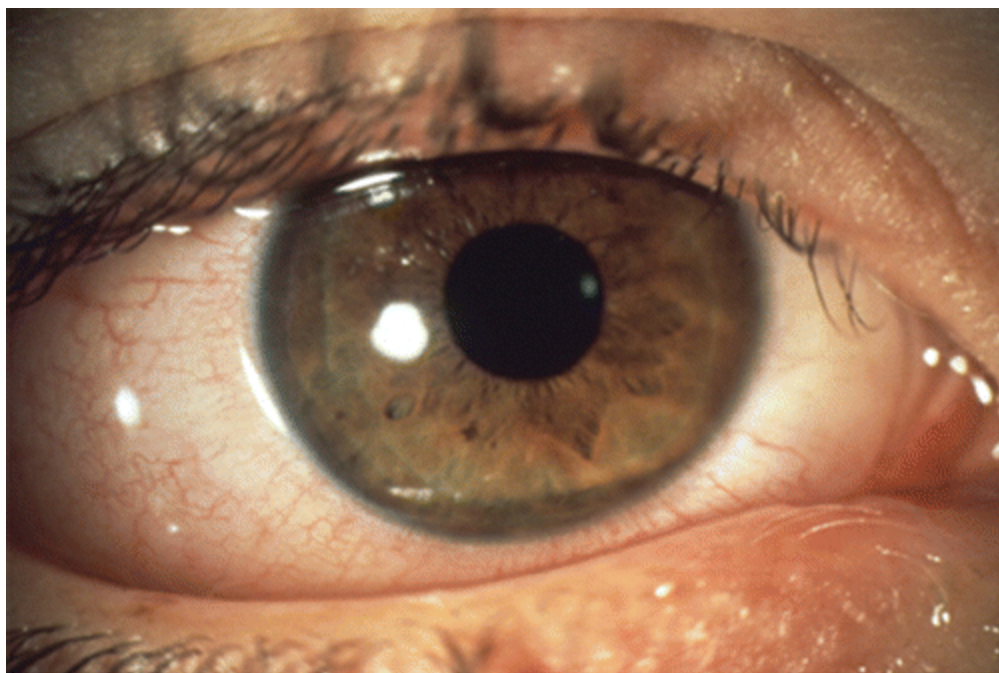


3—Dry eye, severe (courtesy of Allergan, Inc., © 2003)

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7 Severe dry eye can result from failure to properly diagnose and treat dry eye diseases. Severe damage to eye tissue, particularly the corneal surface, can occur (see Chapter 28). (Photograph courtesy of Allergan, Inc., Irvine, California.)



4—Conjunctivitis, allergic (courtesy of Alcon Labs)

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8 Allergic conjunctivitis is characterized by itchy, red eyes with a watery discharge. Vision is usually not impaired, but it may be blurred because of excessive tearing (see Chapter 28).

Color Plate-6



7—Fluorosis, dental

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9 Dental fluorosis (mottled enamel) can develop during the time of tooth formation in children who receive higher than optimal intake of fluoride. Discoloration of the teeth varies, depending on the level of fluoride in the water, and ranges from white flecks or spots to brownish stains, small pits, or deep irregular pits that are dark brown in color (see Chapter 31).



8—Gingivitis, chronic

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10 Chronic gingivitis, an asymptomatic inflammation of the gingivae (gums) at the necks of the teeth, is an early stage of periodontitis and is usually caused by poor oral hygiene. The gingivae are erythematous (red) and may have areas that appear swollen and glossy. In addition, mild bleeding may occur during toothbrushing (see Chapter 31).



9—Periodontitis, chronic

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11 Chronic periodontitis (pyorrhea), an inflammation of the tissues surrounding the teeth, including the gingivae, periodontal ligaments, alveolar bone, and the cementum (bony material covering the root of a tooth), is caused by plaque accumulation resulting from poor oral hygiene. The gingivae may be erythematous and swollen, and may recede from the necks of the teeth. The condition is not painful and usually is accompanied by halitosis, loosening of the teeth, and mild bleeding during toothbrushing (see Chapter 31).



10—Candidiasis, oral

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12 Candidiasis (candidosis, moniliasis, thrush), an infection caused by overgrowth of *Candida albicans*, tends to occur in people with debilitating or chronic systemic disease or those on long-term antibiotic therapy. Candidiasis commonly manifests as a whitish-gray to yellowish, soft, slightly elevated pseudomembrane-like plaque on the oral mucosa; the plaque is often described as having a milk curd appearance. If the membrane is stripped away, a raw bleeding surface remains. A dull, burning pain is often present (see Chapters 31 and 32).



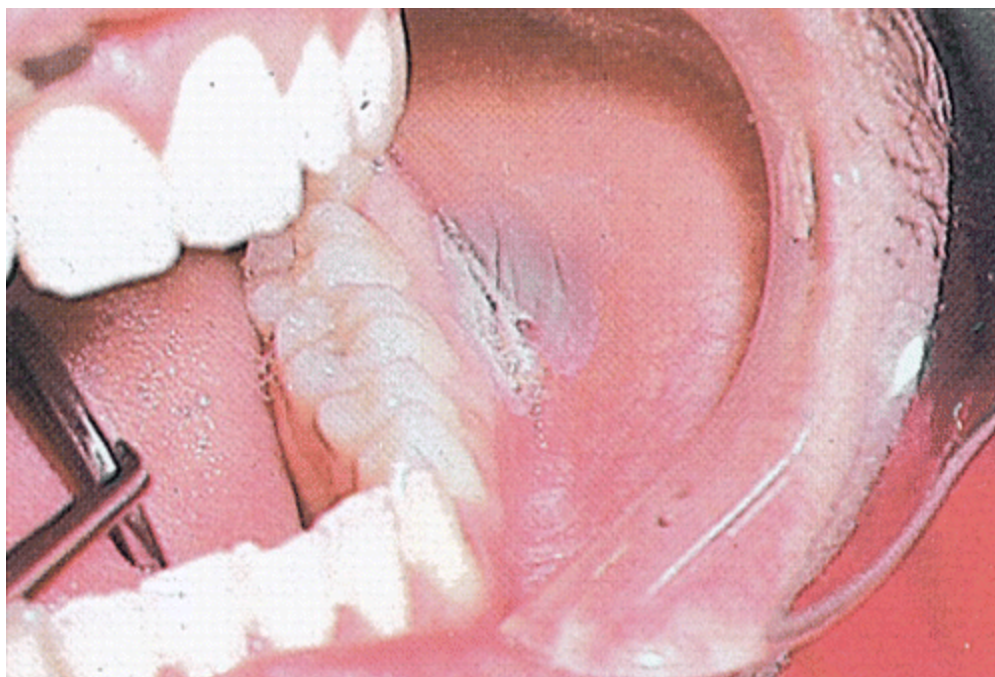
12—Recurrent aphthous ulcers

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13 Recurrent aphthous ulcers (canker sores) are recurrent, painful, single, or multiple ulcerations of bacterial origin. The central ulceration is sharply demarcated, often has a gray to grayish-yellow surface of necrotic debris, and is surrounded by an erythematous margin (see Chapter 32).

Color Plate-7



11—Aspirin burn of oral cavity

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14 Aspirin burn results from the topical use of aspirin to relieve toothache. An aspirin tablet is placed against the tooth, where it is held in place by pressure from the buccal (cheek) mucosa. The mucosa becomes necrotic and is characterized by a white slough that rubs away, revealing a painful ulceration (see Chapter 32).

15 Herpes simplex lesions of the mouth and the eye usually start as a small cluster of vesicles (tiny blisters) that subsequently heal over with a serosanguineous (blood-tinged) crust. Local stinging, burning, and pain often herald the onset of lesions. Eye involvement should always be referred to an ophthalmologist (see Chapter 32).

16A, B, and C Atopic dermatitis (eczema) is an inflammatory condition that occurs **(A)** on the extensor surface of the elbows and knees during the first year of life and then **(B)** involves predominantly the flexors. **C**, The hands,

feet, and face are often involved as well. The dermatitis is characterized by erythema, scale, increased skin surface markings, and crusting; secondary infection is common (see Chapter 33).

17 Seborrheic dermatitis is a red scaling condition of the scalp, midface, and upper midchest of adults. This dermatitis is marked by characteristic greasy, yellowish scaling and is associated with erythema (see Chapter 34).

Color Plate-8

18A, B, and C Psoriasis is a scaling condition in which erythematous plaques (red raised areas) are covered by a thick adherent scale. The borders of the lesions are well developed and vary from guttate (very small drop-shaped plaques) to much larger plaques: **(A)** guttate, **(B)** medium-size plaques, **(C)** large plaques (see Chapter 34).

19A, B, and C Poison ivy, oak, and sumac account for the majority of plant-induced allergic contact dermatitis. **A**, In the United States, poison ivy is the most common of the three plants. It usually grows as a scrambling shrub or a climbing hairy vine that often grows up poles, trees, and building walls. Its leaves are usually large, broad, and spoon-shaped. **B**, Two species of poison oak are indigenous to the United States; both possess leaves with unlobed edges that look similar to those of oak trees. Eastern poison oak (*Toxicodendron toxicarium*) commonly displays three leaflets, whereas Western poison oak (*Toxicodendron diversilobum*) has between 3 and 11 leaflets per stem. Poison oak usually grows as a shrub capable of reaching heights of 131 feet (40 meters). **C**, Poison sumac (*Toxicodendron vernix*) grows in remote areas of the eastern one third of the United States in peat bogs and swampy areas. It grows as a shrub or small tree and attains a height of about 9.8 feet (3 meters). Its pinnate leaves have smooth edges that come to a tip and may be almost 16 inches (40 cm) in length. The leaves are odd numbered, ranging between 7 and 13 leaflets (see Chapter 35). (Photographs courtesy of George Yatskievych, PhD, Missouri Botanical Garden, St. Louis, © 2000.)

Color Plate-9

20A, B, and C **Poison ivy** dermatitis is often associated with **(A)** fluid-filled vesicles (blisters) or bullae, depending on a person's sensitivity. **B**, Streaks of vesicles that correspond to the points of urushiol contact from the damaged plant are highly suggestive of poison ivy exposure. **C**, Oozing and weeping of the vesicular fluid occur for several days, until the affected area develops crusts and begins to dry. Similar reactions can also be caused by poison oak and poison sumac (see Chapter 35). (Photographs courtesy of Christopher Huerter, MD, Creighton University Medical Center, Omaha, Nebraska, © 2002.)

21 **Diaper dermatitis** presents as erythema of the groin (crease area around the genitals) and is common in infants. The case shown here was caused by a contact allergen. Contact irritants, such as urine and feces, and secondary bacterial and yeast infections may also cause problems in this area (see Chapter 36). (Photograph reprinted with permission from emedicine.com, Inc., © 2003.)

22 **Miliaria rubra (heat rash)** is an obstruction of sweat glands. Superficial involvement results in only tiny vesicles (blisters) appearing on the skin surface (miliaria crystallina). When deeper inflammation is present, the surrounding erythema is characteristic of miliaria rubra (see Chapter 36). (Photograph reprinted with permission from emedicine.com, Inc., © 2003.)

Color Plate-10

23 **Scabies** is caused by a small mite that burrows under the superficial skin layers. Small linear blisters that cause intense itching can be seen between the finger webs, on the inner wrists, in the axilla, around the areola (nipple) of the breast, and on the genitalia (see Chapter 37). (Photograph reprinted with permission from emedicine.com, Inc., © 2003.)

24 Ticks can attach to human skin and burrow into superficial skin layers. With careful examination, the back of the organism is usually visible on the skin surface. Ticks are vectors of several systemic diseases (see Chapter 37).

25A and B Pediculus humanus capitis is a louse infestation of the scalp. **A**, Examination of the scalp hair in this infestation shows tiny nits (eggs) attached to the hair shaft. **B**, The organism shown is only occasionally seen (see Chapter 37).

26 Comedonic acne (noninflammatory) occurs when follicles become plugged with sebum, forming a comedone on the surface. The black color is caused by oxidation of lipid and melanin, not dirt as is commonly believed (see Chapter 38).

27 Pustular acne (inflammatory) presents as inflamed papules that are formed when superficial hair follicles become plugged and rupture at a deeper level. Superficial inflammation results in pustules; deep lesions cause large cysts to form with possible resultant scarring (see Chapter 38).

Color Plate-11

28 Sunburn presents as an erythema that occurs after excessive sun exposure; severe burns can result in large blister formation. Proper sunscreen application can provide photoprotection for susceptible patients (see Chapters 39 and 41).

29 Drug-induced photosensitivity is a reaction that occurs on sun-exposed surfaces of the head, neck, and dorsum (back) of the hands. The erythema does not occur on photoprotected areas, such as under the nose and chin, behind the ears, and between the fingers (see Chapter 39).

30 Cosmetic-induced photosensitivity can be caused by ingredients in certain topical colognes and perfumes. This reaction produces a local

erythema that leaves characteristic postinflammatory pigmentation (see Chapter 39).

31 Tinea pedis infection of the toes characteristically starts between the fourth and fifth web space and spreads proximally. Scaling can progress to maceration with resultant small fissures (see Chapter 42).

32 Tinea capitis, a fungal infection of the scalp, is marked by scale on the scalp with local breaking or loss of hair; erythema (redness) is usually not observed (see Chapter 42).

Color Plate-12

33 Common warts are viral-induced lesions that present as localized rough accumulations of keratin (hyperkeratosis) containing many tiny furrows. If the wart's surface is pared, small bleeding points can be seen (see Chapter 43).

34 Plantar warts, caused by a viral infection, are often found on the plantar surface of the foot and present with hard, localized accumulations of keratin. The punctate bleeding points seen when the lesions are pared distinguish plantar warts from calluses (see Chapter 43). (Photograph reprinted with permission from emedicine.com, Inc., © 2003.)

35 Calluses are thickened scales that often form on joints and weight-bearing areas. A callus on the plantar surface of the foot is shown here (see Chapter 44).

Updates

Content Update for “Preface”

- Removal of the pregnancy risk categories for all drugs and natural products, and subsequently, the removal of the two appendices that focused on pregnancy risk information.

The following explains the reasoning for this decision:

In 2015 the Food and Drug Administration (FDA) implemented the Pregnancy and Lactation Labeling Rule (PLLR), which replaces the former pregnancy risk letter categories (A, B, C, D, X) for prescription drugs with more descriptive content in the following fields^{1,2}:

- Pregnancy: now includes labor and delivery
- Lactation
- Females and males of reproductive potential

Although this new categorization provides clinicians with more detail for decision making, clinicians still need to apply this information on a case-by-case basis. The PLLR will be implemented in phases, with the final phase to be completed by June 29, 2018. However, this rule is not applicable to self-care and nonprescription products.

Previous editions of the *Handbook* have included pregnancy risk letter designations, where available, and oftentimes this was based on the designation for the prescription version of the medication. With the changes that have taken place and the lack of support for letter designations to identify pregnancy risk, the editors decided to remove any reference to a pregnancy risk category within chapters, and to remove both appendices. Where this information appeared previously we now include general language that supports the reader in determining, based on available literature, what is best for their particular patient in each situation. The following is the standard language in all chapters that mention medication or product use in pregnancy:

- See the Preface for a detailed explanation of the pregnancy data.

- Use in pregnancy should be limited to clinical situations in which the potential benefit justifies potential risk to the fetus

Where a pregnancy issue exists for a nonprescription product, the Drug Facts Label states that the consumer should ask a health care professional before using the product if she is pregnant or breastfeeding. FDA is aware of the limitations of the Drug Facts Label for communicating complex issues such as pregnancy labeling. They attempt to ensure nonprescription labeling is as consistent as possible with the prescription drug labels when a drug is available in both forms. However, the challenge with nonprescription products is to provide information that consumers can understand but is detailed enough to address any concerns. FDA is aware of the inconsistencies this situation has created and, at the time of this writing, was discussing options to enhance the pregnancy content for nonprescription products.