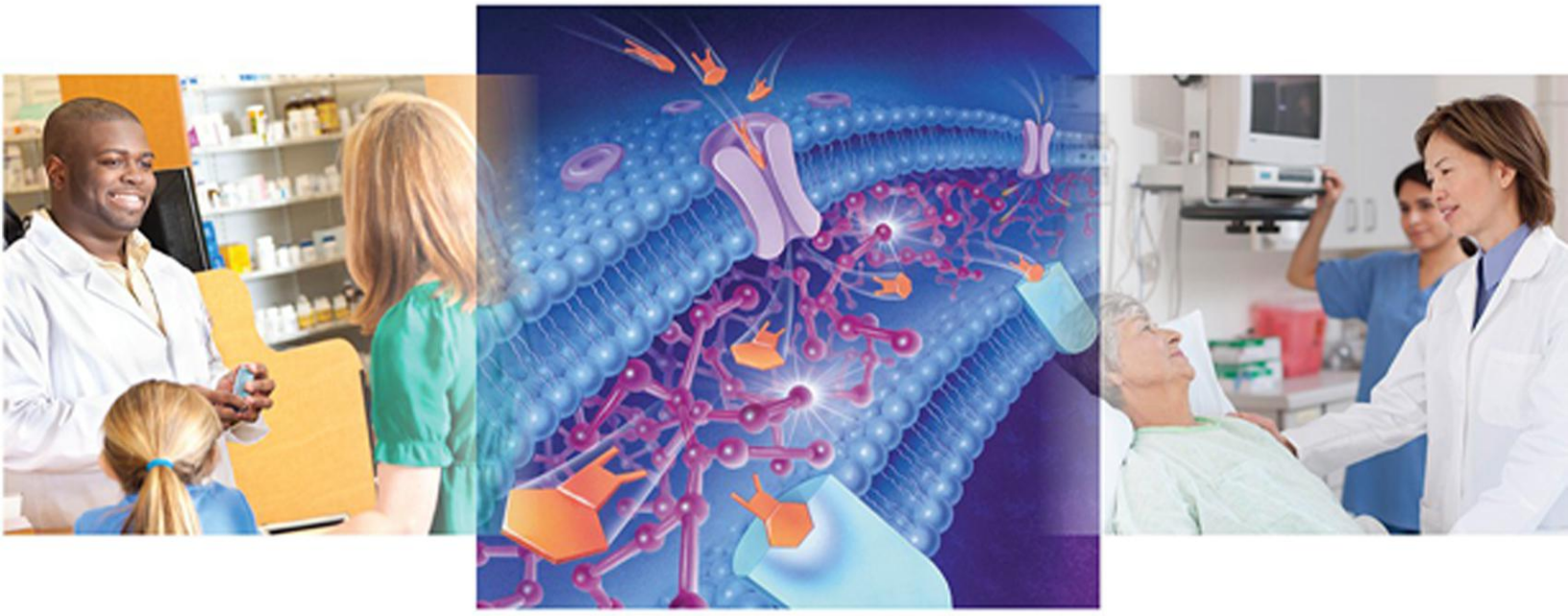
FOURTH EDITION

Pharmacotherapy

PRINCIPLES & PRACTICE



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Mc Graw Hill Education

Pharmacotherapy Principles & Practice

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Pharmacotherapy Principles & Practice

FOURTH EDITION

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PREFACE

Use of effective and safe pharmacotherapy is a cornerstone of appropriate patient care for both acute and chronic medical conditions. Although the biomedical research enterprise continues to provide medications that have enormous potential to improve individual patient and population health outcomes, these agents are too often applied inappropriately and ineffectively. Consequently, many patients do not achieve the best possible outcomes or incur harm from their drug therapy.

Appropriate implementation and management of high-quality, cost-effective pharmacotherapy by health care providers requires an integration of scientific knowledge and clinical practice skills combined with a fiduciary responsibility to put the patient's needs first. The development of mature, independent pharmacotherapists occurs through structured learning processes that include formal coursework, independent study, mentorship, and direct involvement in the care of actual patients in interprofessional settings.

The fourth edition of *Pharmacotherapy Principles & Practice* is designed to provide student learners and health care practitioners with essential knowledge of the pathophysiology and pharmacotherapeutics of disease states likely to be encountered in routine practice. Chapters are written by content experts and peer reviewed by clinical pharmacists, nurse practitioners, physician assistants, and physicians who are authorities in their fields.

Pharmacotherapy Principles & Practice, fourth edition, opens with an introductory chapter followed by chapters on pediatrics, geriatrics, and palliative care. The remainder of the book consists of 98 disease-based chapters that review disease etiology, epidemiology, pathophysiology, and clinical presentation, followed by clear therapeutic recommendations for drug selection, dosing, and patient monitoring. The following features were designed in collaboration with educational design specialists to enhance learning and retention:

- *Structured learning objectives* at the beginning of each chapter, with information in the text that corresponds to each learning objective identified by a vertical rule in the margin, allowing the reader to quickly find content related to each objective.
- *Key concepts related to patient assessment and treatment* highlighted with an easily identifiable icon throughout the chapter.
- *Patient encounters* that facilitate development of critical thinking skills and lend clinical relevance to the scientific foundation provided.
- A new section on the *patient care process* that provides specific recommendations about the process of care for an individual patient, from the initial patient assessment through therapy evaluation, care plan development, and follow-up monitoring.
- *Up-to-date literature citations* for each chapter to support treatment recommendations.
- *Tables, figures, and algorithms* that enhance understanding of pathophysiology, clinical presentation, medication selection, pharmacokinetics, and patient monitoring.
- *Medical abbreviations and their meanings* at the end of each chapter to facilitate learning the accepted shorthand used in real-world health care settings.
- *Self-assessment questions and answers for each chapter* in the Online Learning Center to facilitate self-evaluation of learning.
- *Laboratory values* expressed as both conventional units and Système International (SI) units.
- *Appendices* that contain: (1) conversion factors and anthropometrics; (2) common medical abbreviations; (3) glossary of medical terms (the first use of each term in a chapter appears in bold, colored font); and (4) prescription writing principles.
- *A table of common laboratory tests and reference ranges* appears on the inside covers of the book.

A companion textbook, *Pharmacotherapy Principles and Practice Study Guide: A Case-Based Care Plan Approach,* is available to further enhance learning by guiding students through the process of applying knowledge of pharmacotherapy to specific patient cases. This study guide contains approximately 100 patient cases that correspond to chapters published in the textbook.

The Online Learning Center at www.ChisholmPharmacotherapy.com provides self-assessment questions, grading and immediate feedback on the questions, and reporting capabilities. The complete textbook and study guide are now available to subscribers of the publisher's AccessPharmacy site (www.accesspharmacy.com), an online educational resource for faculty and students of the health professions.

We acknowledge the commitment and dedication of more than 185 contributing authors and more than 65 peer reviewers of the chapters in this new edition. We are also grateful to many educators and institutions that have adopted this text in their courses. Finally, we extend our sincere thanks to the McGraw-Hill Professional editorial team, especially Michael Weitz, Peter Boyle, and Laura Libretti, for their dedication in bringing this new edition to you.

The Editors
February 2016

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Part I

Basic Concepts of Pharmacotherapy Principles and Practices

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1 Introduction

Jack E. Fincham

INTRODUCTION

Health professionals are given significant responsibilities in our health care system. These roles may be taken for granted by patients until a pharmacist, nurse practitioner, physician assistant, physician, or others perform assigned tasks that make major impacts upon patients and patients' families lives in countless ways. The exemplary manner in which health professionals provide necessary care to patients is a hallmark of health professional practice and delivery of US health care. Patients are thus well served, and fellow health professionals share knowledge and expertise specific to their profession. However, there are significant problems remaining in the US health care system from a structural standpoint. The United States spends 17% to 18% of the gross domestic product (GDP) on health care, yet the United States ranks 37th in the world considering outcomes of care. Comparing the United States to similar industrialized countries, we rank 11th out of 11 comparator contries.[1]

The uninsured remain a major concern. There were close to 45.2 million uninsured individuals in the United States in 2012, representing 16.9% of the population.[2] This significant number exists despite the institution of health care reform in the United States beginning in 2010. Even with health care reform, the number of uninsured younger than 65 years has decreased only 1.3%. Simply stated, this uninsured segment of the US population is simply staggering in scope and implications for the future collective health of the US population.

Countless other Americans in our midst are underinsured. They may have partial coverage after a fashion, but for these Americans the high price of deductibles, co-pays, and monthly payments for insurance create an economic dilemma for individuals each time they seek care or pay premiums. Recent expenditure data indicate that in 2013, $3.8 trillion was spent on health care in the United States during 2013[3] and $329.2 billion was spent for prescriptions.[4]

There are tremendous opportunities for health professionals due to the implementation the Patient Protection and Affordable Care Act (PPACA). For the first time in the structure of the US health care system, there is a tangible, significant effort to enhance the quality and outcomes of health care delivered. Now payment mechanisms are in place to demand the evidence of quality of health care delivered, regardless of point of delivery of services. If the quality is not there, reimbursement will be decreased, increased, or stay static in monetary values provided to providers.[5] The intent of these measures is to reduce and/or eliminate unnecessary expenditures and duplicative health care service in the United States.

The use of medications in the health care system provides enormous help to many; lives are saved or enhanced, and life spans are lengthened. Many other uses of medications lead to significant side effects, worsening states of health, and premature deaths. So, how to separate these disparate pictures of drug use outcomes? You, within your practices and within your networks in the health care workplace, can help to promote the former and diminish the latter. The authors of the chapters in this book have written informative, current, and superb chapters that can empower you to positively influence medication use.

DRUG USE IN THE HEALTH CARE SYSTEM

Spending on drugs, as a percentage of what was spent on health care in total, increased 3.2% in 2013 compared to the previous year.[6] Drivers for this significant increase include increasing numbers of therapy innovative products and price increases for agents not facing patent expirations.

Prescription medications are used daily; 48.5% of the population uses one prescription drug daily, 21.7% use three or more drugs daily, and 10.6% use five or more prescription drugs daily.[2] Problems occurring with the use of drugs can include:

- Medication errors
- Suboptimal drug, dose, regimen, dosage form, and duration of use
- Unnecessary drug therapy
- Therapeutic duplication
- Drug–drug, drug–disease, drug–food, or drug–nutrient interactions
- Drug allergies
- Adverse drug effects, some of which are preventable

Clinicians are often called upon to resolve problems that occur due to undertreatment, overtreatment, or inappropriate treatment. Individuals can purchase medications through numerous outlets. Over-the-counter (OTC) medications can be purchased virtually anywhere. OTCs are widely used by all age groups. Prescription medications can be purchased through traditional channels (community chain and independent pharmacies), from mail-order pharmacies, through the Internet, from physicians, from health care institutions, and elsewhere. Herbal remedies are marketed and sold in numerous outlets. The monitoring of positive and negative outcomes of the use of these drugs, both prescription and OTC, can be disjointed and incomplete. Clinicians and health professionals need to take ownership of these problems and improve patient outcomes resulting from drug use.

Although clinicians are the gatekeepers for patients to obtain prescription drugs, patients obtain prescription medications from numerous sources. Patients may also borrow from friends, relatives, or even casual acquaintances. In addition, patients

obtain OTC medications from physicians through prescriptions, on advice from pharmacists and other health professionals, through self-selection, or through the recommendations of friends or acquaintances. Through all of this, it must be recognized that there are both formal (structural) and informal (word-of-mouth) components at play. Health professionals may or may not be consulted regarding the use of medications, and in some cases are unaware of the drugs patients are taking.

External variables may greatly influence patients and their drug-taking behaviors. Coverage for prescribed drugs allows those with coverage to obtain medications with varying cost-sharing requirements. However, many do not have insurance coverage for drugs or other health-related needs.

Self-Medication

Self-medication can be broadly defined as a decision made by a patient to consume a drug with or without the approval or direction of a health professional. The self-medication activities of patients have increased dramatically in the late 20th and early 21st centuries. Many factors affecting patients have continued to fuel this increase in self-medication. There have been many prescription items switched to OTC classification in the last 50 years, which is dramatically and significantly fueling the rapid expansion of OTC drug usage. In addition, patients are increasingly comfortable with self-diagnosing and self-selection of OTC remedies.

Through the rational use of drugs, patients may avoid more costly therapies or expenditures for other professional services. Self-limiting conditions, and even some chronic health conditions (eg, allergies and dermatologic conditions), if appropriately treated through patient self-medication, allow the patient to have a degree of autonomy in health care decisions.

Compliance Issues

Noncompliance with prescription regimens is one of the most understated problems in the health care system. Approximately 10% of initial prescriptions written by physicians are never filled.[6] Reasons can include trying too soon to obtain a new prescription, prior approval requirements, the prescribed drug may not be covered under the patient's insurance, etc. The effects of noncompliance have enormous ramifications for patients, caregivers, and health professionals. Noncompliance is a multifaceted problem with a need for interprofessional, multidisciplinary solutions. Interventions that are organizational (how clinics are structured), educational (patient counseling, supportive approach), and behavioral (impacting health beliefs and expectations) are necessary. Compliant behavior can be enhanced through your actions with the patients for whom you provide care. Sometimes what is necessary is referral to specific clinicians for individualized treatment and monitoring to enhance compliance. The case histories provided in this textbook will allow you to follow what others have done in similar situations to optimally help patients succeed in improving compliance rates and subsequent positive health outcomes.

Drug Use by the Elderly

The major source of payment for prescription drugs for those aged 65 years and older in the United States is the Medicare Part D Drug Benefit. Seniors have benefitted tremendously from this component. Estimates place the expenditure for Medicare Part D to be $58 billion in 2014; this is 11% of Medicare expenditures.[7] Since the inception of Medicare Part D, recipients have had to pay costs after initial minimum threshold amounts are reached, then enter the so-called "donut hole" requiring payment out of pocket until a certain amount would be paid, and then coverage for payment would ensue. This so called donut hole closes in 2020, which will provide more benefits for more enrollees. At that point, estimates place Medicare Part D payments to account for 16% of Medicare expenditures.[7] Enhanced use of pharmacoeconomic tenets to select appropriate therapy, while considering cost and therapeutic benefits for seniors and others, will become even more crucial for clinicians in the future.

Unnecessary drug therapy and overmedication are problems with drug use in the elderly. Cost estimates are projected to be $1.3 billion per year for elderly patient polypharmacy alone.[4] A joint effort by health professionals working together is the best approach to aiding seniors in achieving optimal drug therapy. Evaluation of all medications taken by seniors at each patient visit can help prevent polypharmacy from occurring.[8]

IMPACTING THE PROBLEMS OF DRUG USE

Medication Errors

There is a tremendous opportunity in medication use and monitoring for working to reduce medication errors. Untold morbidity and mortality occur due to the many errors occurring in medication use. Studies have shown that reconciling the medications that patients take, with coordination by various caregivers providing care, can help reduce medication errors in patient populations.[11] Current changes in how drugs are prescribed, such as electronic prescribing, bar code identification of patients, and electronic medication records, can and have helped to reduce medication errors.[9,10]

The incorporation of three key interventions (computerized physician order entry [CPOE], additional staffing, and bar coding) have been shown in an institutional setting to help reduce medication errors.[10] Being able to track drug ordering, dispensing, and administration electronically has been shown to be cost-effective in the long run.[11] Nurses and office staff have been proven as a valuable resource for reporting prescribing errors, especially with ongoing reminders to scrutinize orders.[12]

HEALTH CARE REFORM

The potential for health care reform to enhance patient outcomes and the quality of care provided to Americans is very significant. The inclusion of health professionals in segments of the innovative medical homes and accountable care organizations will help all health care providers reach more patients needing care.[13]

DiPiro and Davis[14] noted that now and in the future, there will be an important and expectant need for pharmacists to focus on health outcomes and documentation of quality to fully participate in the new health care models that are a focus of health care reform. These authors point to accountable care organizations and patient centered medical homes as innovative models for health professionals to more fully participate.

There are also covered preventive aspects enabled by the PPACA that include immunizations, screenings, and other offering. The provision of these preventive activities by health professionals will serve patients over the long term and work to prevent costly care later on.

SUMMARY

Health professionals are at a crucial juncture facing an uncertain, yet promising future. Technological advances, including electronic prescribing, may stem the tide of medication errors and inappropriate prescribing. These technological enhancements

for physician order entry (via personal data assistants or through web access to pharmacies) have been implemented to reduce drug errors. The skills and knowledge that enable effective practice have never been more daunting among the numerous health professions. Technology can further empower health professionals to play an effective role in helping patients and fellow health professionals to practice safe and effective medicine. Health care reform has the potential to dramatically impact your practices in the health care system for the length of your careers. There is also current, and no doubt future, enhanced use of health care apps available to consumers. Consumer computer apps have pervaded many aspects of society, including health care.[15] Consumer apps, although many in number, have not gained widespread use at present; it may be that there are simply too many in number and their utility has not yet been widely adopted.

The use of this text, which incorporates materials written by the finest minds in pharmacy practice and education, can enable the reader to play a crucial role in improving the drug use process for patients, providers, payers, and society. The thorough analysis of common disease states, discussion of therapies to treat these conditions, and specific advice for patients will help you in your practices. The purpose of this book is to help you make a real improvement in the therapies you provide to your patients. Current and future clinicians can rely on the information laid out here to enhance your knowledge and allow you to assist your patients with the sound advice that they expect you to provide. Use the text, case histories, and numerous examples here to expand your therapeutic skills, and to help positively impact your patients in the years to come.

You can help to reverse medication-related problems, improve outcomes of care both clinically and economically, and enable drug use to meet stated goals and objectives. This text provides a thorough analysis and summary of treatment options for commonly occurring diseases and the medications or alternative therapies used to successfully treat these conditions.

Abbreviations Introduced in This Chapter

CPOE	computerized physician order entry
GDP	gross domestic product
OTC	over-the-counter
PPACA	Patient Protection and Affordable Care Act

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2 Geriatrics

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Explain changing aging population demographics.
2. Discuss age-related pharmacokinetic and pharmacodynamic changes.
3. Identify drug-related problems and associated morbidities commonly experienced by older adults.
4. Describe major components of geriatric assessment.
5. Recognize interprofessional patient care functions in various geriatric practice settings.

INTRODUCTION

The growth of the aging population and increasing lifespan require that health care professionals gain knowledge necessary to meeting the needs of this patient group. Despite the availability and benefit of numerous pharmacotherapies to treat their diseases, older patients commonly experience drug-related problems resulting in additional morbidities. Therefore, it is essential for clinicians serving older adults across all health care settings to understand the epidemiology of aging, age-related physiological changes, drug-related problems prevalent in the elderly, comprehensive geriatric assessment, and interprofessional approaches to geriatric care.

EPIDEMIOLOGY AND ETIOLOGY

As humans age, they are at increasing risk of disease, disability, and death for three reasons: (a) genetic predisposition; (b) reduced immunological surveillance; and (c) the accumulated effects of physical, social, environmental, and behavioral exposures over the life course. All elders experience increasing vulnerability (**homeostenosis**) as they age, resulting in considerable heterogeneity in health states and care requirements. While resilient elders can maintain high levels of physical and cognitive functioning, others suffer functional decline, **frailty**, disability, or premature death. There is an urgent need for all clinicians to better understand the epidemiology of aging to comprehensively provide high-value services to optimize functioning and health-related quality of life of older adults.[1]

Sociodemographics

▸ *Population*

KEY CONCEPT *Our population is rapidly growing older.* In 2010, 40.3 million US residents were 65 years and older (13% of the total population), nearly 5.5 million people were 85 years or older (the "oldest-old"), and over 53,000 were centenarians.[2] The baby boomers (those born between 1946 and 1964) began turning 65 years in 2011; their numbers will double to 83.7 million in the year 2050, representing over 20% of the total US population.[3] In 2010, there were a total of 22.9 million women and 17.4 million men (an average ratio of 100 women to 77.3 men) 65 years and older; this ratio widens as elders age. The oldest-old are projected to increase from 5.3 million in 2006 to nearly 21 million in 2050.[3] In addition, minority elders are projected to increase to 12.9 million in 2020.[3] Surviving baby boomers will be disproportionally female, more ethnically/racially diverse, better educated, and have more financial resources than were elders in previous generations.

▸ *Economics*

More elders are enjoying higher economic prosperity than ever before, although major inequalities persist, with older blacks and those without high school diplomas reporting fewer financial resources.[4] Considerable disparities exist, and may prevent less advantaged elders from being able to purchase all prescribed medications.

▸ *Education and Health Literacy*

By 2007, more than 75% of US elders had graduated from high school, and nearly 20% had a bachelor's degree or higher. Still, substantial educational differences exist among racial and ethnic minorities. While more than 80% of non-Hispanic white elders had high school degrees in 2007, 72% of Asians, 58% of blacks, and 42% of Hispanic elders were graduates. Nearly 40% of people 75 years or older have low **health literacy**, more than any other age group.[4] Despite these limitations, the Pew Trust reports that more than 8 million Americans (22%) 65 years or older increasingly use the Internet,[5] and large health care systems are increasingly offering online health information to older health consumers. These advances are important because communication between health care providers and elders is vital in providing quality care, supporting self-care, and in negotiating transitions of care.

Health Status

▶ *Life Expectancy*

Although Americans are living longer than ever before, an estimated average of 78.14 years overall in 2008, US life expectancy lags behind that of many other industrialized nations.[6] There is nearly a 6-year gap between 2008 estimated life expectancy in men (75.29 years) and women (81.13 years).[6] Disparities in mortality persist, with estimated 2008 life expectancy in the white population nearly 5 years higher than that of the black population.[6] Nearly 35% of US deaths in 2000 were attributed to three risk behaviors: smoking, poor diet, and physical inactivity. Currently, only 9% of Americans older than 65 years smoke; however, nearly 54% of men and 21% of women are former smokers.[7] Overweight elders 65 to 74 years of age increased from 57% to 73% in 2004 largely due to inactivity and a diet high in refined foods, saturated fats, and sugared beverages.[4] Despite the proven health benefits of regular physical activity, more than half of the older population is sedentary; 47% of those 65 to 74 years and 61% older than 75 years report no physical activity.[8]

The 2007 National Health Interview Survey indicated that 39% of non-Hispanic white elders reported "very good" or "excellent" health, compared with 29% of Hispanics and 24% of blacks.[9] Approximately 80% of older adults have at least one chronic condition, and 50% have at least two. The prevalence of certain chronic conditions differs by sex, with women reporting higher levels of arthritis (54% vs 43%), and men reporting higher levels of heart disease (37% vs 26%) and cancer (24% vs 19%).[5] Among the 15 leading causes of death, age-adjusted death rates decreased significantly from 2004 to 2005 for the top three leading causes: heart disease (33%), cancer (22%), and stroke (8%); while rates of chronic lower respiratory diseases, unintentional injuries, Alzheimer disease, influenza and pneumonia, hypertension, and Parkinson disease increased.[6] Figure 2–1 specifies the most common chronic conditions of older adults by sex. Frailty is a common biological syndrome in the elderly. Once frail, elders may rapidly progress toward failure to thrive and death. Only 3% to 7% of elders between the ages of 65 and 75 years are frail, increasing to more than 32% in those older than 90 years.[10]

Patient Encounter, Part 1

CC is an 80-year-old woman who lived in Mexico until just after her 67th birthday when she moved to the United States to take care of her grandchildren. Her daughter was promoted at work and required more travel, so asked CC for help with the children. CC finished eighth grade in Mexico, speaks almost no English, therefore has low health literacy. She was referred to the Interprofessional Geriatrics Clinic for a comprehensive care of multiple chronic conditions, including hypertension, diabetes, stroke, seizure disorder, arthritis, depression, insomnia, and glaucoma. CC uses 14 medications for the described conditions and supplements from Mexico for "general health." She is overweight and reports eating high amount of refined foods because she cooks for her grandchildren only. She watches TV most of the day while the kids are at school.

What information is consistent with epidemiology of aging?

Which of CC's medical conditions are commonly found in older adults?

What additional information do you need before conducting a comprehensive medication review?

▶ *Health Care Utilization and Cost*

KEY CONCEPT *Older Americans use more health care services than younger Americans do.* Although hospital stays for those 65 years and older decreased by half from 1970 to 2010 (12.6 vs 5.5 days), they accounted for more than 65% of hospitalizations overall, with longer lengths of stay corresponding to increasing age.[11] In 2010 there were 1.3 million (3.6%) US nursing home residents aged 65 and older, and as the aged live longer, more will require assistance, which will be increasingly performed in the home. Health care costs among older Americans are three to five times greater than the cost for someone younger than 65 years.

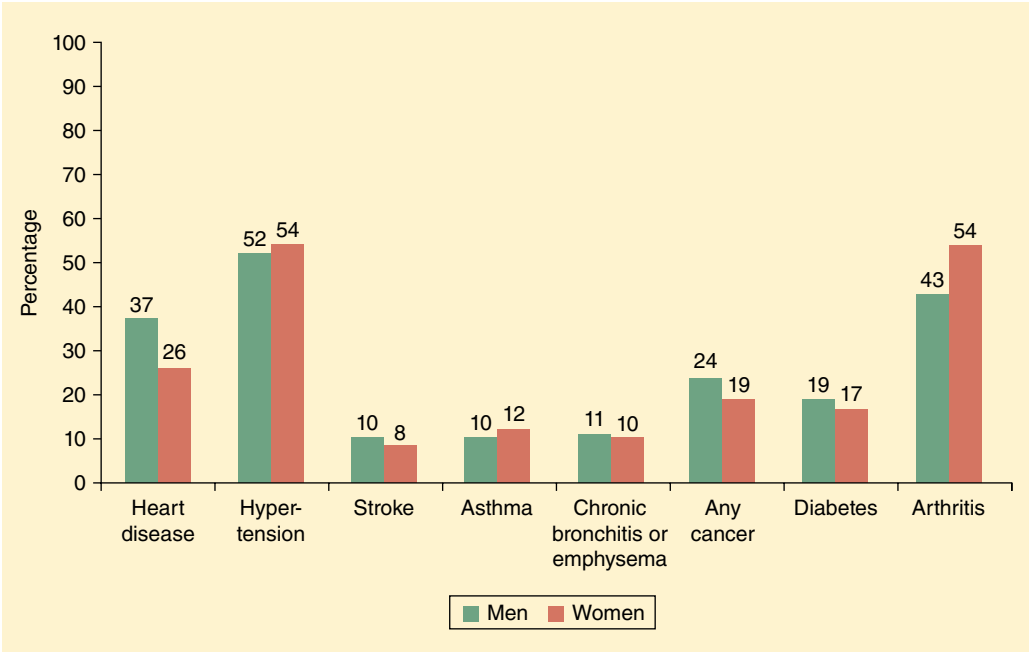


FIGURE 2–1. Percentage of people 65 years and older who reported having selected chronic conditions, by sex, 2005 to 2006. Note: Data are based on a 2-year average from 2005 to 2006. Reference population: These data refer to the noninstitutionalized population. (From Centers for Disease Control and Prevention, National Center for Health Statistics, National Health Interview Survey.)

Medicare plays a major role in health care costs, accounting for 20% of total US health spending in 2012, 27% of spending on hospital care, and 23% of spending on physician services.[12]

By applying the epidemiology of aging, clinicians can better intervene with pharmacotherapy to postpone disease, disability, and mortality, and promote health, functioning, and health-related quality of life.

AGE-RELATED CHANGES

In basic terms, pharmacokinetics is what the body does to the drug, and pharmacodynamics is what the drug does to the body. KEY CONCEPT *All four components of pharmacokinetics—absorption, distribution, metabolism, and excretion—are affected by aging; the most clinically important and consistent is the reduction of renal elimination of drugs.*[13] As people age, they can become more frail and are more likely to experience altered and variable drug pharmacokinetics and pharmacodynamics. Even though this alteration is influenced more by a patient's clinical state than their chronological age, the older patient is more likely to be malnourished and suffering from diseases that affect pharmacokinetics and pharmacodynamics.[14] Clinicians have the responsibility to use pharmacokinetic and pharmacodynamic principles to improve the care of older patients and avoid adverse effects of pharmacotherapy.

Pharmacokinetic Changes

▸ *Absorption*

Multiple changes occur throughout the gastrointestinal (GI) tract with aging, but little evidence indicates that drug absorption is significantly altered. The changes include decreases in overall surface of the intestinal epithelium, gastric acid secretion, and splanchnic blood flow.[13] Peristalsis is weaker and gastric emptying delayed. These changes slow absorption in the stomach, especially for enteric-coated and delayed-release preparations. Delays in absorption may lead to a longer time required to achieve peak drug effects, but it does not significantly alter the amount of drug absorbed, and drug movement from the GI tract into circulation is not meaningfully changed.[13,14] However, relative **achlorhydria** can decrease the absorption of nutrients such as vitamin B_{12}, calcium, and iron.[14]

Aging facilitates atrophy of the epidermis and dermis along with a reduction in barrier function of the skin. Tissue blood perfusion is reduced, leading to decreased or variable rates of transdermal, subcutaneous, and intramuscular drug absorption. Therefore, intramuscular injections should generally be avoided in the elderly due to unpredictable drug absorption.[13] Additionally, because saliva production decreases with age, medications that need to be absorbed rapidly by the buccal mucosa are absorbed at a slower rate.[14] Yet, for most drugs, absorption is not significantly affected in older patients and the changes described are clinically inconsequential.[15]

▸ *Distribution*

Main physiological changes that affect distribution of drugs in older adults are changes in body fat and water, and in protein binding. Lean body mass can decrease by 12% to 19% through loss of skeletal muscle in the elderly. Thus, blood levels of drugs primarily distributed in muscle increase (eg, digoxin), presenting a risk for overdose.[14] While lean muscle mass decreases, adipose tissue can increase with aging by 18% to 36% in men and 33% to 45% in women. Therefore, fat-soluble drugs (eg, diazepam, amiodarone, and verapamil) have increased volume of distribution (V_d), leading to higher tissue concentrations and prolonged duration of action. Greater V_d leads to increased half-life and time required to reach steady-state serum concentration.[13,14]

Total body water decreases by 10% to 15% by age 80. This lowers V_d of hydrophilic drugs (eg, aspirin, lithium, and ethanol) leading to higher plasma drug concentrations than in younger adults when equal doses are used.[13,14] Toxic drug effects may be enhanced when dehydration occurs and when the extracellular space is reduced by diuretic use.

Likewise, plasma albumin concentration decreases by 10% to 20%, although disease and malnutrition contribute more to this decrease than age alone.[13] In patients with an acute illness, rapid decreases in serum albumin can increase drug effects. Examples of highly protein-bound drugs include warfarin, phenytoin, and diazepam.[14] For most chronic medications, these changes are not clinically important because although the changes affect peak level of a single dose, mean serum concentrations at steady state are not altered unless clearance is affected.[14] For highly protein-bound drugs with narrow therapeutic indices (eg, phenytoin), however, it is important to appropriately interpret serum drug levels in light of the older patient's albumin status. In a malnourished patient with hypoalbuminemia, a higher percentage of the total drug level consists of free drug than in a patient with normal serum albumin. Thus, if a hypoalbuminemic patient has a low total phenytoin level and the phenytoin dose is increased, the free phenytoin concentration may rise to a toxic level.[15]

▸ *Metabolism*

Drug metabolism is affected by age, acute and chronic diseases, and drug–drug interactions. The liver is the primary site of drug metabolism, which undergoes changes with age; though the decline is not consistent, older patients have decreased metabolism of many drugs.[13,15] Liver mass is reduced by 20% to 30% with advancing age, and hepatic blood flow is decreased by as much as 40%. These changes can drastically reduce the amount of drug delivered to the liver per unit of time, reduce its metabolism, and increase the half-life.[14] Metabolic clearance of some drugs is decreased by 20% to 40% (eg, amiodarone, amitriptyline, warfarin, and verapamil), but it is unchanged for drugs with a low hepatic extraction.[14] Drugs that have high **extraction ratios** have significant first-pass metabolism, resulting in higher bioavailability for older adults. For example, the effect of morphine is increased due to a decrease in clearance by around 33%. Similar increases in bioavailability can be seen with propranolol, levodopa, and statins. Thus, older patients may experience a similar clinical response to that of younger patients using lower doses of these medications.[14]

The effect of aging on liver enzymes (cytochrome P-450 system [CYP450]) may lead to a decreased elimination rate of drugs that undergo oxidative phase I metabolism, but this is controversial.[13] Originally, it was thought that the CYP450 system was impaired in the elderly, leading to decreased drug clearance and increased serum half-life, but studies have not consistently confirmed this. Thus, variations in the CYP450 activity may not be due to aging but to lifestyle (eg, smoking), illness, or drug interactions.[14,15] A patient's nutritional status plays a role in drug metabolism as well. Frail elderly have a more diminished drug metabolism than those with healthy body weight.[13] Aging does not affect drugs that undergo phase II hepatic metabolism, known as conjugation or glucuronidation, but conjugation is reduced with frailty. Temazepam and lorazepam are examples of drugs that undergo phase II metabolism.[14]

▶ Elimination

The clinically most important pharmacokinetic change in the elderly is the decrease in renal drug elimination.[13] As people age, renal blood flow, renal mass, glomerular filtration rate, filtration fraction, and tubular secretion decrease. After age 40, there is a decrease in the number of functional glomeruli, and renal blood flow declines by approximately 1% yearly. From age 25 to 85 years, average renal clearance declines by as much as 50% and is independent of the effects of disease.[13–15] Still, the impact of age on renal function is variable and not always linear.[15] Longitudinal studies have suggested that a percentage (up to 33%) of older adults do not experience this age-related decline in renal function. Clinically significant effects of decreased renal clearance include prolonged drug half-life, increased serum drug level, and increased potential for **adverse drug reactions** (ADRs).[13] Special attention should be given to renally eliminated drugs with a narrow therapeutic index (eg, digoxin, aminoglycosides). Monitoring serum concentration and making appropriate dose adjustment for these agents can prevent serious ADR resulting from drug accumulation.[14] It is important to note that despite a dramatic decrease in renal function (creatinine clearance) with aging, serum creatinine may remain fairly unchanged and remain within normal limits. This is because elderly patients, especially the frail elderly, have decreased muscle mass resulting in less creatinine production for input into circulation.[13,14] Because chronic kidney disease can be overlooked if a clinician focuses only on the serum creatinine value, overdose and ADR can occur.

Thus, creatinine clearance should be calculated when starting or adjusting pharmacotherapy in older adults. Clearance measure using 24-hour urine collection is impractical, costly, and often done inaccurately. The Cockcroft–Gault equation is the most widely used formula for estimating renal function and adjusting drug doses. See Chapter 25 (Table 25–2) for more details.

$$\text{Creatinine clearance} = \frac{(140 - \text{Age}) \times \text{Weight (kg)}}{\text{Serum creatinine} \times 72} \times (0.85 \text{ if female})$$

when serum creatinine is expressed in mg/dL,

$$\text{CrCl (mL/min)} = \frac{(140 - \text{Age}) \times 1.23 \times (\text{BW})}{(\text{SCr})} (\times 0.85 \text{ if women})$$

When serum creatinine is expressed in μmol/L, and converted to units of mL/s by multiplying by 0.167.

This equation is also used by drug manufacturers to determine renal dosing guidelines. The Cockcroft–Gault equation provided the best balance between predictive ability and bias in a study that compared it with the Modification of diet in renal disease (MDRD) and Jelliffe "bedside" clearance equations.[14] Understand that the predictive formulas can significantly overestimate actual renal function in chronically ill, debilitated older patients.

Pharmacodynamic Changes

Pharmacodynamics refers to the actions of a drug at its target site and the body's response to that drug. KEY CONCEPT *In general, the pharmacodynamic changes that occur in the elderly tend to increase their sensitivity to drug effects.* Most pharmacodynamic changes in the elderly are associated with a progressive reduction in homeostatic mechanisms and changes in receptor properties. Although the end result of these changes is an increased sensitivity to the effects of many drugs, a decrease in response can also occur.[16] The changes in the receptor site include alterations in binding affinity of the drug, number or density of active receptors at the target organ, structural features, and postreceptor effects (biochemical processes/signal transmission). These include receptors in the adrenergic, cholinergic, and dopaminergic systems, as well as γ-*aminobutyric acid* (GABA) and opioid receptors.[13,14]

▶ Cardiovascular System

Decreased homeostatic mechanisms in older adults increase their susceptibility to orthostatic hypotension when taking drugs that affect the cardiovascular system and lower the arterial blood pressure. This is explained by a decrease in arterial compliance and baroreceptor reflex response, which limits their ability to compensate quickly for postural changes in blood pressure. It has been estimated that 5% to 33% of the elderly experience drug-induced orthostasis. Examples other than typical antihypertensives that have a higher likelihood of causing orthostatic hypotension in geriatric patients are tricyclic antidepressants, antipsychotics, loop diuretics, direct vasodilators, and opioids.[13,14,16] Older patients have a decreased β-adrenergic receptor function, and they are less sensitive to β-agonists and β-adrenergic antagonists effects in the cardiovascular system and possibly in the lungs, but their response to α-agonists and antagonists is unchanged.[14,16] Increased hypotensive and heart rate response (to a lesser degree) to calcium channel blockers (eg, verapamil) are reported. Increased risk of developing drug-induced QT prolongation and **torsade de pointes** is also present.[16] Therefore, clinicians must start medications at low doses and titrate slowly, closely monitoring the patient for any adverse effects.

▶ Central Nervous System

Overall, geriatric patients exhibit a greater sensitivity to the effects of drugs that gain access to the CNS. In most cases, lower doses result in adequate response, and higher incidence of adverse effects may be seen with standard and high doses. For example, lower doses of opioids provide sufficient pain relief for older patients, whereas conventional doses can cause oversedation and respiratory depression.[13,14,16] The blood-brain barrier becomes more permeable as people age; thus, more medications can cross the barrier and cause CNS adverse effects. Examples of problematic medications include benzodiazepines, antidepressants, neuroleptics, and antihistamines. There is a decrease in the number of cholinergic neurons as well as nicotinic and muscarinic receptors, decreased choline uptake from the periphery, and increased acetylcholinesterase.[14,16] The elderly have a decreased ability to compensate for these imbalances of the neurotransmitters, which can lead to movement and memory disorders. Older adults have an increased number of dopamine type 2 receptors, making them more susceptible to delirium from anticholinergic and dopaminergic medications. At the same time, they have a reduced number of dopamine and dopaminergic neurons in the substantia nigra of the brain, resulting in higher incidence of extrapyramidal symptoms from antidopaminergic medications (eg, antipsychotics).[13,16]

▶ Fluids and Electrolytes

Fluid and electrolyte homeostatic mechanism is decreased in the geriatric population. The elderly experience more severe dehydration with equal amounts of fluid loss compared with younger adults.

The multitude of factors involved include decreased thirst and cardiovascular reflexes, decreased fluid intake, decreased ability of the kidneys to concentrate urine, increased atrial natriuretic peptide, decreased aldosterone response to hyperkalemia, and decreased response to antidiuretic hormone. The result is an increased incidence of hyponatremia, hyperkalemia, and prerenal azotemia, especially when the older patient is taking a diuretic (eg, hydrochlorothiazide, furosemide). Angiotensin-converting enzyme inhibitors have an increased potential to cause hyperkalemia and acute renal failure in older adults. Thus, these agents need to be started with low doses, titrated slowly, and monitored frequently.[13,16]

▸ *Glucose Metabolism*

An inverse relationship between glucose tolerance and age has been reported. This is likely due to reduced insulin secretion and sensitivity (greater insulin resistance). Consequently, the incidences of hypoglycemia are increased when using sulfonylureas (eg, glyburide, glipizide) from age-related impairment to counterregulate the hypoglycemic response.[13] Due to an impaired autonomic nervous system, elderly patients may not distinguish symptoms of hypoglycemia such as sweating, palpitations, or tremors. They do experience neurological symptoms of syncope, ataxia, confusion, or seizures.

▸ *Anticoagulants*

Older people are more sensitive to anticoagulant drug effects compared to younger people. When similar plasma concentrations of warfarin are attained, there is greater inhibition of vitamin K–dependent clotting factors in older patients than in younger counterparts. Overall, the risk of bleeding is increased in the elderly, and when overanticoagulated, the likelihood of morbidity and mortality is higher. This is further complicated by the presence of **polypharmacy**, drug–drug interactions, non-adherence, and acute illness. Close monitoring of the **international normalized ratio** (INR) and appropriate use is paramount. In contrast, there is no association between age and response to heparin.[13]

Patient Encounter, Part 2

CC was recently hospitalized for dehydration and is recovering from "low kidney function." CC's daughter (interpreter) states that one of the providers thought CC may need to double her phenytoin dose. CC's current chronic medications include: (1) losartan 50 mg by mouth twice daily, (2) amlodipine 5 mg by mouth twice daily, (3) hydrochlorothiazide 25 mg by mouth every morning, (4) sertraline 50 mg by mouth at bedtime, (5) glyburide 5 mg by mouth twice daily, (6) phenytoin 100 mg by mouth three times a day, (7) zolpidem 10 mg by mouth at bedtime, (8) calcium-vitamin D 600 mg–500 units by mouth twice daily, (9) oxycodone-acetaminophen 5–325 mg two tablets by mouth every 4 hours for pain, (10) brimonidine 0.1% one drop in each eye twice daily, (11) brinzolamide 1% one drop in each eye twice daily, (12) timolol 0.5% one drop in each eye twice daily, (13) bimatoprost 0.3% one drop in each eye at bedtime, (14) diphenhydramine 25 mg by mouth at bedtime. She is allergic to penicillin (hives) and experienced cough with lisinopril. CC does not smoke or drink alcohol.

VS: BP: 102/52, P: 68 beats/min, RR: 14, T: 38.4°C (101.1°F)

Ht: 5′2″ (157 cm), Wt: 66 kg, Pain: 0/10

Labs: Na 141 mEq/L (141 mmol/L), K 4.2 mEq/L (4.2 mmol/L), Cl 98 mEq/L (98 mmol/L), CO_2 25 mEq/L (25 mmol/L), BUN 55 mg/dL (19.6 mmol/L), creatinine 1.6 mg/dL (141 µmol/L), glucose 98 mg/dL (5.4 mmol/L), albumin 2.7 g/dL (27 g/L), $HgbA_{1c}$ 6.6% (0.066; 49 mmol/mol Hgb), phenytoin 10 mcg/mL (mg/L; 40 µmol/L)

What is CC's estimated creatinine clearance?

What steps should be taken prior to increasing CC's phenytoin dose?

What drug-related problems does CC have per her medication list?

DRUG-RELATED PROBLEMS

KEY CONCEPT *Comorbidities and polypharmacy complicate elderly health status, particularly inappropriate medications that lead to drug-related problems.* It is reported that 28% of hospitalizations in older adults are due to medication-related problems, including nonadherence and ADRs. Studies also indicate that 14% to 40% of the frail elderly are prescribed at least one inappropriate drug, and unnecessary medication use was detected in 44% of older veterans at the time of hospital discharge.[17] A decision-tree model estimated the overall cost of drug-related morbidity and mortality in 2000 as greater than $177.4 billion, with $121.5 billion (almost 70%) for hospital admissions and $32.8 billion (18%) for long-term care admissions.[18] Collaboration among interprofessional providers and older patients can ensure appropriate therapy, minimize adverse drug events, and maximize medication adherence.

Polypharmacy

Polypharmacy is defined as taking multiple medications concurrently (four to nine medications or more have been used as criteria in studies). Polypharmacy is prevalent in older adults who compose 14% of the US population but receive 36.5% of all prescription drugs.[17] An estimated 50% of the community-dwelling elderly take five or more medications, and 12% of them take 10 or more.[19] Also, common use of dietary supplements and herbal products in this population adds to polypharmacy. In nursing home settings, patients receiving nine or more chronic medications increased from 17% in 1997 to 27% in 2000.[17] Among various reasons for polypharmacy, an apparent one is a patient receiving multiple medications from different providers who treat the patient's comorbidities without coordinated care. Thus, medication reconciliation becomes increasingly important as the aging population continues to grow.

A review analyzing studies aimed at reducing polypharmacy in elderly emphasized complete evaluation of all medications by health care providers at each patient visit to prevent inappropriate polypharmacy.[20] Efforts should be made to reduce polypharmacy by discontinuing any medication without indication. However, clinicians should also understand that appropriate polypharmacy is indicated for older adults who have multiple diseases, and support should be provided for optimal adherence. Drug-related problems associated with polypharmacy can be identified by performing a comprehensive medication review (see Patient Care Process).

Inappropriate Prescribing

Inappropriate prescribing is defined as prescribing medications that cause a significant risk of an adverse event when there is an effective and safer alternative. The incidence of prescribing potentially inappropriate drugs to elderly patients has been reported to be 12% in those living in the community and 40% in nursing home residents.[21,22] A systematic review in 2012 reported that the median rate of inappropriate medication prescribing among elderly patients in the primary care setting was 19.6%.[23] At times, medications are continued long after the initial indication has resolved. The clinician prescribing for older adults must understand the rate of adverse reactions and drug–drug interactions, the evidence available for using a specific medication, and patient use of over-the-counter (OTC) medications and herbal supplements.[21]

Screening tools have been developed to help the clinician identify potentially inappropriate medications in older adults. The most utilized is the Beers criteria,[24] first developed in 1991. The current Beers criteria include 53 medications or medication classes that are potentially inappropriate in elderly patients, listed in three categories: (a) medications that should be avoided regardless of disease/condition, (b) potentially inappropriate medications when used in older adults with certain diseases/syndromes, and (c) medications to use with caution.[24]

Common medications referred to in the Beers criteria are as follows:[24]

- Tertiary tricyclic antidepressants (TCAs) like amitriptyline (strong anticholinergic and sedative properties)
- Benzodiazepines including diazepam (increased risk of falls, fractures, and cognitive impairment)
- First-generation antihistamines like diphenhydramine (confusion and fall risk with prolonged effect)
- Nonsteroidal anti-inflammatory drugs (NSAIDs) (increased risk of GI bleeding, exacerbate heart failure, and cause kidney injury)

Examples of drug/disease combinations reported as potentially inappropriate:

- Anticholinergic drugs in patients with bladder outlet obstruction or benign prostatic hyperplasia
- Metoclopramide and antipsychotics in patients with Parkinson disease and antipsychotics in patients with dementia
- Benzodiazepines, anticholinergics, antispasmodics, and muscle relaxants with cognitive impairment

Practical strategies for appropriate medication prescribing include establishing a partnership with patients and caregivers to enable them to understand and self-monitor their medication effects. Providers should perform drug–drug and drug–disease interaction screening, use time-limited trials to evaluate the benefits and risks of new regimens, and trial off medications to assess need.[23]

Undertreatment

Much has been written about the consequences of overmedication and polypharmacy in the elderly. However, underutilization of medications is just as harmful, resulting in reduced functioning, and increased morbidity and mortality. There are instances when a drug is truly contraindicated, when a lower dose is indicated, or when prognoses dictate withholding therapy. Outside of these scenarios, many elders do not receive therapeutic interventions that would provide benefit.[25] This occurs for many reasons, including belief that treatment of primary problem is enough intervention, cost, concerns of nonadherence, fear of adverse effects and associated liability, starting low and failing to increase to an appropriate dose, skepticism regarding secondary prevention benefits, or **ageism**. A study found underprescribing in 64% of older patients, and those on more than eight medications at the highest risk. Interestingly, the lack of proven beneficial therapy did not depend on age, race, sex, comorbidity, cognitive status, and dependence in activities of daily living.[26] Common categories of geriatric undertreatment are listed in **Table 2–1**.

Table 2–1

Common Categories of Geriatric Undertreatment

Therapy	Concern
Anticoagulation in patients with atrial fibrillation	Overly concerned with risk of bleeding or the risk of falls if anticoagulated
Malignant and nonmalignant pain complaints	Hesitant to prescribe opioids due to possible cognitive and bowel side effects, concerns about addiction; patients may often be hesitant to take opioids
Antihypertensive therapy	Underestimate the benefit on stroke and cardiovascular event prevention, and/or fail to add the second or third medication needed to attain control
β-Blocker treatment in heart failure	Concerned about complications in high-risk patients despite the substantial evidence of mortality benefit
Statin treatment for ASCVD	Underestimate benefit or have concerns about adverse events

ASCVD, atherosclerotic cardiovascular disease.

A clinical assessment to weigh the potential benefit versus harm of the older patient's complete medication regimen is required. Once obvious contraindications have been dismissed, the patient's (a) goals and preferences, (b) prognosis, and (c) time to therapeutic benefit should be taken into consideration to determine whether the pharmacotherapy meets treatment goals. Underprescribing can best be avoided by using clinical assessment strategies, improving adherence support, and liberalizing financial coverage of drugs.

Adverse Drug Reaction

ADR is defined by the World Health Organization as a reaction that is noxious and unintended, which occurs at dosages normally used in humans for prophylaxis, diagnosis, or therapy. (See the glossary for the American Society of Health-System Pharmacists' definition of an ADR.[27]) ADRs increase with polypharmacy use and are the most frequently occurring drug-related problem among elderly nursing home residents. The yearly occurrence in outpatient older adults is 5% to 33%.[28]

Seven predictors of ADRs in older adults have been identified[28]: (a) taking more than four medications; (b) more than 14-day hospital stay; (c) having more than four active medical problems; (d) general medical unit admission versus geriatric ward; (e) alcohol use history; (f) lower Mini Mental State Examination

Table 2–2

Strategies to Prevent Adverse Drug Reactions in Older Adults

- Evaluating comorbidities, frailty, and cognitive function
- Identifying caregivers to take responsibility for medication management
- Evaluating renal function and adjusting doses appropriately
- Monitoring drug effects
- Recognizing that clinical signs or symptoms can be an ADR
- Minimizing number of medications prescribed
- Adapting treatment to patient's life expectancy
- Realizing that self-medication and nonadherence are common and can induce ADRs

ADR, adverse drug reaction.

Adapted, with permission, from Merle L, Laroche ML, Dantoine T, et al. Predicting and preventing adverse drug reactions in the very old. Drugs Aging. 2005;22(5):375–392.

score (confusion, dementia); and (g) two to four new medications added during a hospitalization. Similarly, there are four predictors for severe ADRs experienced by the elderly[29]: (a) use of certain medications, including diuretics, NSAIDs, antiplatelet medications, and digoxin; (b) number of drugs taken; (c) age; and (d) comorbidities. Suggested strategies to preventing ADRs in older adults are described in Table 2–2.[29] Particular caution must be taken when prescribing drugs that alter cognition in the elderly, including antiarrhythmics, antidepressants, antiemetics, antihistamines, anti-Parkinson, antipsychotics, benzodiazepines, digoxin, histamine-2 receptor antagonists, NSAIDs, opioids, and skeletal muscle relaxants.[29]

One of the most damaging ADRs that frequently occur in older adults is medication-related falls. Falls are associated with a poor prognosis ranging from premature institutionalization to early death, and polypharmacy is a risk factor. A systematic review concluded that psychotropic medications, including benzodiazepines, antidepressants, and antipsychotics have a strong association with increased risk of falls, while antiepileptics and antihypertensives have a weak association.[30] Comprehensive fall prevention strategies should include medication simplification and modification to prevent or resolve ADRs.

Nonadherence

America's other drug problem is the term given to medication nonadherence by the National Council on Patient Information and Education.[31] Nonadherence to chronic medications is prevalent and escalates health care costs associated with worsening disease and increased hospitalization.[31] *Medication adherence* describes a patient's medication-taking behavior, generally defined as the extent to which one adheres to an agreed regimen derived from collaboration with their health care provider.[32]

KEY CONCEPT *Older adults are at greater risk for medication nonadherence due to the high prevalence of multimorbidities, cognitive deficit, polypharmacy, and financial barriers.* Numerous barriers to optimal medication adherence exist and include patient's lack of understanding, provider's failure to educate, polypharmacy leading to **complex regimen** and inconvenience, treatment of asymptomatic conditions (such as hypertension and dyslipidemia), and cost of medications.[32] Factors influencing medication nonadherence are listed in Table 2–3.

Table 2–3

Factors Influencing Medication Nonadherence

Three or more chronic medical conditions	Significant cognitive or physical impairments
Five or more chronic medications	Recent hospital discharge
Three times or more per day dosing or 12 or more medication doses per day	Caregiver reliance
	Low health literacy
	Medication cost
Four or more medication changes in past 12 months	History of medication nonadherence
Three or more prescribers	Living alone in the community

Following is a list of six "how" questions to ask when assessing medication adherence[33]:

1. How do you take your medicines?
2. How do you organize your medicines to help you remember to take them?
3. How do you schedule your meal and medicine times?
4. How do you pay for your medicines?
5. How do you think the medicines are working for your conditions?
6. How many times in the last week/month have you missed your medicine?

Although no single intervention has found to improve adherence consistently, patient-centered multicomponent interventions such as combining education, convenience, and regular follow-up have resulted in a positive impact on medication adherence and associated health outcomes.[34] Future research needs include adherence studies evaluating belief-related variables, such as personal and cultural beliefs, in larger and more ethnically diverse samples of older populations.

Patient Encounter, Part 3

CC is now 90 years old and has been living at a long-term care facility for a year. Even though she was overweight most of her life, she has lost 5 kg in the past 6 months and developed a new coccyx ulcer. She is currently on multiple medications, including (1) aspirin 81 mg by mouth daily, (2) hydrochlorothiazide 25 mg by mouth twice daily, (3) metformin 500 mg by mouth twice daily, (4) levothyroxine 25 mcg by mouth daily, (5) ibuprofen 600 mg by mouth daily, (6) docusate sodium 100 mg by mouth twice daily, (7) lorazepam 2 mg by mouth three times daily, (8) diphenhydramine 25 mg by mouth at bedtime, and (9) amitriptyline 10 mg by mouth at bedtime. Today her pain score is 7/10.

What recommendations can be made about CC's medication regimen at this time?

Which quality indicators should be of concern in CC?

GERIATRIC ASSESSMENT

The term *geriatric assessment* is used to describe the interprofessional team evaluation of the frail, complex elderly patient. Such a team may include but is not limited to a geriatrician, nurse, pharmacist, case manager/social worker, physical therapist, occupational therapist, speech therapist, psychologist, dietician, dentist, optometrist, and audiologist. Assessment may be performed in a centralized geriatric clinic or by a series of evaluations performed in separate settings after which the team may conduct an interprofessional case conference to discuss the patient's assessment and plan.

Patient Interview

KEY CONCEPT *The clinical approach to assessing older adults frequently goes beyond a traditional "history and physical" used in general internal medicine practice.*[35] Functional status must be determined, which includes the activities of daily living (ADLs) and instrumental activities of daily living (IADLs), see Table 2–4. Evidence of declining function in specific organ systems is sought. Of particular importance is cognitive assessment, which may require collateral history from family, friends, or other caregivers, and is important in determining the patient's capacity to consent to medical treatment.[36] The mini-cog mental status examination,[37] shown in Figure 2–2, is a quick tool to assess patient's cognitive impairment. Commonly there is decreased visual acuity, hearing loss, dysphagia, and impaired dexterity. Decreased skin integrity, if present, greatly increases risk for pressure ulcers. Sexual function is a sensitive but important area and should be specifically inquired about. Cardiac, renal, hepatic, and digestive insufficiencies can have significant implications for pharmacotherapy. Inadequate nutrition may lead to weight loss and impaired functioning at the cellular or organ level. See Table 2–5 for common problems experienced by older adults.

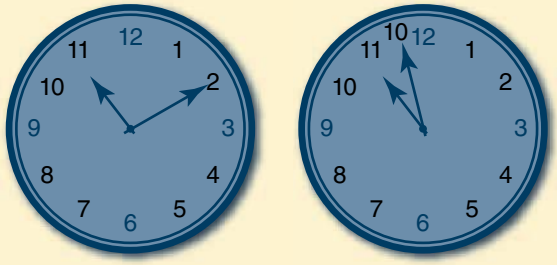
It is important to recognize "geriatric syndromes" such as frailty, falls, osteoporosis, insomnia, and incontinence that have an impact on quality of life. Common diseases present with atypical symptoms, such as thyroid dysfunction and depression presenting as delirium. It is also important to assess for caregiver

Three-item recall

1. Ask the patient if you may test his or her memory.
2. Give the patient three words (eg, apple, table, penny) to repeat and remember.
3. Have the patient repeat the three words from memory later (eg, after the clock drawing test).

Clock drawing test

1. Have the patient draw the face of a clock, including numbers.
2. Instruct the patient to place the hands at a specific time, such as 11:10.



Correct | Incorrect hands and inserted number

A positive dementia screen

1. Failure to remember all three words.
2. Failure to remember one or two words plus an abnormal clock drawing.

FIGURE 2–2. The mini-cog mental status examination. (Adapted from Borson S, Scanlan J, Brush M, Vitaliano P, Dokmak A. The mini-cog: A cognitive "vital signs" measure for dementia screening in multi-lingual elderly. Int J Geriatr Psychiatry. 2000;15(11):1021–1027.)

Table 2–4

Activities of Daily Living and Instrumental Activities of Daily Living

ADLs			
Transfers	Dressing	Mobility	Eating
Bathing	Toileting	Grooming	
IADLs			
Using transportation	If still driving, assess driving ability (including cognitive function, medications that can impair driving ability, vision, neuromuscular conditions that may interfere with reaction time, ability to turn head) at the time of license renewal		
Using the telephone	Check for emergency phone numbers located near the telephone		
Management of finances	Assess the ability to balance checkbook and pay bills on time		
Cooking	Check for safe operation of appliances and cooking tools as well as ability to prepare balanced meals		
Housekeeping	Check for decline in cleanliness or neatness		
Medication administration	Assess organization skills and adherence		

ADL, activity of daily living; IADL, instrumental activity of daily living.

Table 2–5

The *I*s of Geriatrics: Common Problems in Older Adults

Immobility	Instability
Isolation	Intellectual impairment
Incontinence	Impotence
Infection	Immunodeficiency
Inanition (malnutrition)	Insomnia
Impaction	Iatrogenesis
Impaired senses	

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stress and be aware of older patients' support systems. These may include family, friends, religious and social networks, as well as home health aides, homemakers, or sitters. Such networks may facilitate older adults to continue to live independently. Home safety assessment is often necessary for the frail elderly. In addition, look for signs and symptoms of elder abuse, neglect, or exploitation. Health professionals are required to report suspicion of elder mistreatment to Adult Protective Services.[38]

Drug Therapy Monitoring

Geriatric patients often are frail and have multiple medications, medical comorbidities, and prescribers. It is essential that there be a single provider who oversees the patient's pharmacotherapy. The providers need to be aware of the patient's Medicare Part C or D plan, and what type of coverage these plans afford. What is the copayment for generic, preferred, and nonpreferred drugs? Is the patient responsible for all drug costs during the Medicare "donut hole" period? (The first $2250 of medication is partially subsidized, but the patient pays 100% of the next $2850.[39]) Many Medicare patients, especially the socioeconomically challenged, have limited understanding of the complex Medicare drug benefit. This problem is compounded when the prescriber also does not understand the patient's insurance program.[40] Providers can assist patients by prescribing generic medications that are offered through retail pharmacy discount plans ($4 retail pharmacy programs do not bill insurance, thus are not counted toward the $2250 Medicare benefit) and help patients apply for the medication assistance programs offered by drug manufacturers. Particularly challenging in the geriatric population is identifying the cause(s) of nonadherence. Providers assessing older patients' medication regimens should keep the following questions in mind:

- Are medications skipped or reduced due to cost?
- Can the patient benefit from sample drugs? Starting a patient on a free drug sample may increase patient costs in the long term because samples typically are newer, expensive drugs.[40]
- Is there an educational barrier such as low health literacy?
- Does the patient speak English but only read in another language?
- Can the patient see labels and written instructions?
- Does the patient have hearing problems? Patients might not admit they cannot hear instructions.
- Can the patient manipulate pill bottles, syringes, inhalers, eye/ear drops?
- Has the patient's cognitive functioning worsened over time such that they can no longer follow the medication regimen?

Homeostenosis and comorbidities require more frequent monitoring for adverse effects: symptoms, abnormal laboratory results, drug interactions, and drug levels.

Documentation

A clear, current, and accurate medication list must be available to the patient and all individuals involved with their care. It is particularly important for geriatric patients to bring medication containers for reconciliation by a provider. Medications taken may require verification with the pharmacist, caregivers, or family. Transitions in patient care, such as hospital to subacute nursing facility or home, are points of vulnerability for medication errors because medications may have been deleted or added.[41] It is now standard of care to conduct medication reconciliation upon hospital admission and discharge to ensure that the medication list is up to date.

Patient Education

Poor adherence in the geriatric age group could be related to inadequate patient education. "Ask me 3" cues the patient to ask three important questions of their providers to improve health literacy[42]:

1. What is my main problem?
2. What do I need to do?
3. Why is it important for me to do this?

The provider can assess patient grasp of medication instructions by asking the patient to repeat instructions initially and again in 3 minutes (teach-back method).

KEY CONCEPT *Consideration of geriatric patients' vision, hearing, swallowing, cognition, motor impairment, and education and health literacy during counseling and education can lead to enhanced medication adherence.* Specific drug formulations, such as metered-dose inhalers, ophthalmic/otic drops, and subcutaneous injections, will require detailed education and practice. More time needs to be spent on advising the patient and/or caregivers of potential ADRs and when to notify the provider about ADRs also. (See Patient Care Process box for detailed information regarding patient education.)

GERIATRIC PRACTICE SITES

Ambulatory Clinic and Home-Based Primary Care

Ambulatory geriatric clinics are established to provide a multitude of primary care needs specifically tailored to the older population. Home-based primary care brings primary care into the patient's home for homebound patients to facilitate independent living at home as long as possible. Patients are usually referred by their primary care physicians due to the desire for increased access to services (patients-to-physician ratio), complex care needs due to multimorbidity and polypharmacy, and need for geriatric treatment competencies. It is common for the appearance of cognitive impairment to be the catalyst for a referral to such services. Interprofessional team care is the norm in these settings, which benefits patients with varied needs. The interprofessional teams hold regular meetings to discuss care plans of the patients. The geriatrician, who has specialized training in treating the older population encompassing patient's physical, medical, emotional, and social needs assumes the overall care of the patient. The clinical pharmacist focuses on optimizing medication regimen by conducting comprehensive medication review, making evidence-based disease state management recommendations, screening and resolving drug-related problems, and educating patients, caregivers and members of the health care team about pharmacotherapy and monitoring parameters. Clinical pharmacists' effectiveness can be enhanced with the specialty certification in geriatrics. Nurses provide medical triage and day-to-day patient care activities such as obtaining vitals, providing wound care, educating patients, and ensuring adherence. Social workers are involved in various aspects from assessing mood and cognitive status of patients to obtaining placement in higher levels of care. Physical/occupational therapists are often involved in improving the patient's functional status, providing fall prevention interventions, and maintaining a safe home environment. They provide adaptive equipment such as grab bars, raised toilet seat and shower bench for the bathroom, and cane

or walker for ambulation. Dieticians evaluate the patient's nutritional status and educate on proper diet and weight management. Using these team collaborations, specialty geriatric clinics have developed including a multidisciplinary geriatric oncology clinic[43] and a community-based memory clinic.[44]

Long-Term Care

Long-term care provides support for people who are dependent to varying degrees in ADLs and IADLs, numbering about 9 million people older than 65 years in 2008.[45] Care is provided in the patient's home, in community settings such as adult care homes or assisted living facilities, and in nursing homes. Long-term care is expensive, typically several thousand dollars per month. Most care is provided at home by unpaid family members or friends. Medicare covers all or part of the cost of skilled nursing care for a limited period posthospitalization.[45,46] Medicare does not cover long-term care. Financing of long-term care comes from patients' and family savings and/or private long-term care insurance. When a patient's assets have been depleted, Medicaid provides basic nursing home care.[46] However, this care is heavily discounted, often resulting in economizing such as lower caregiver-to-patient ratios and higher number of patients per room. Nursing homes are highly regulated by state and federal government through the Center for Medicare and Medicaid Services.[47]

Initial and continuing certification of the facility depends on periodic state and federal review of the facility. Auditors' ratings are available to consumers in an online Nursing Home Report Card.[47] **Quality indicators** are used by facility administrators and government overseers to identify problem areas, including[48]:

- Use of nine or more medications in single patient
- Prevalence of indwelling catheters
- Prevalence of antipsychotic, anxiolytic, and hypnotic use
- Use of physical restraints
- Prevalence of depression in patients without antidepressant therapy
- Clinical quality measures such as pressure ulcers
- Moderate daily pain or excruciating pain in residents

Long-term care geriatric practices emphasize the interprofessional team approach. The medical director leads regular meetings with all disciplines delivering care. These may include director of nursing, rehabilitation services (physical, occupation, and speech therapy), pharmacist, social worker, nutritionist, case manager, and psychologist. The pharmacist conducts a monthly drug review of each patient's medication list.[41] The physician is alerted to medication concerns and approves the patient's orders every 60 days. Such a team approach is vital to coordinate care for the typical frail, complex long-term care patient.

Patient Care Process

1. Identify drug-related problems in the older patient by performing a comprehensive medication review.
2. Have the patient bring all medication bottles to the visit, including prescription medications, OTC medications, vitamins, supplements, and herbal products.
3. Identify the indication for all medications used by the patient.
4. Review medication doses to determine any underdose and/or overdose.
5. Screen for drug–drug, drug–disease, drug–vitamin/herbal, drug–food interactions.
6. Ensure that patient is not using any agents to which they have allergies or intolerance.
7. Assess medication adherence by using combination methods (whenever possible): tablet/capsule count, refill history, self-report, and demonstration of use of nonoral agents.
8. Inquire about ADRs experienced.
9. Identify untreated indication or undertreatment, including preventive use of aspirin and calcium plus vitamin D.
10. Assess vital signs, including pain.
11. Evaluate laboratory findings to assess renal function, hepatic function, therapeutic drug monitoring (eg, digoxin, warfarin, phenytoin), and therapeutic goals for chronic diseases (eg, $HgbA_{1c}$).
12. Perform medication regimen tailoring when indicated: discontinue unnecessary medications/supplements/herbals, simplify dosing times to minimize complex regimen, and tailor regimen to individual's daily routine to improve adherence.
13. Solve any physical/functional barriers to medication use such as providing non–child-resistant caps and tablet cutters.
14. Provide education and adherence aid:
    - Verbal and written information about medications and/or disease states in health literacy-sensitive manner
    - Specific product education for nonoral agents (eg, inhalers, insulin, ophthalmic/otic drops)
    - Medication chart/list to include generic and brand names, indication, dose, direction for use, timing of dose, etc.
    - Medication storage, expiration date, and refill status
    - Medication organizer (eg, pillbox, blister packs) when indicated
    - List of future appointments
15. Promote self-monitoring and lifestyle modification by promoting use of blood pressure monitoring device and glucometer, diet and exercise, smoking cessation, immunization.
16. Formulate a patient-centered and interprofessional team-based follow-up plan to track patient response and health outcomes, and to prevent adverse events.

Abbreviations Introduced in This Chapter

ADL	Activities of daily living
ADR	Adverse drug reaction
GABA	γ-aminobutyric acid
$HgbA_{1c}$	Hemoglobin A_{1c}
IADL	Instrumental activities of daily living
INR	International normalized ratio
MDRD	Modification of diet in renal disease
NSAID	Nonsteroidal anti-inflammatory drug
OTC	Over the counter
V_d	Volume of distribution

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3 Pediatrics

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LEARNING OBJECTIVES

Upon completion of the chapter, the reader will be able to:

1. Define different age groups within the pediatric population.
2. Explain general pharmacokinetic and pharmacodynamic differences in pediatric versus adult patients.
3. Identify factors that affect selection of safe and effective drug therapy in pediatric patients.
4. Identify strategies for appropriate medication administration to infants and young children.
5. Apply pediatric pharmacotherapy concepts to make drug therapy recommendations, assess outcomes, and effectively communicate with patients and caregivers.

INTRODUCTION

Pediatric clinical practice involves care of infants, children, and adolescents with the goal of optimizing health, growth, and development toward adulthood. Clinicians serve as advocates for this unique and vulnerable patient population to optimize their well-being. Care for pediatric patients is relevant in both inpatient and outpatient settings and requires additional considerations with regards to selection and monitoring of drug therapy.

KEY CONCEPT *Despite the common misconception of pediatric patients as "smaller adults" where doses are scaled only for their smaller size, there are multiple factors to consider when selecting and providing drug therapy for patients in this specific population.* Pediatric patients significantly differ within their age groups and from adults regarding drug administration, psychosocial development, and organ function development, which affect the efficacy and safety of pharmacotherapy.

FUNDAMENTALS OF PEDIATRIC PATIENTS

Classification of Pediatric Patients

Pediatric patients are those younger than 18 years, although some pediatric clinicians may care for patients up to age 21. Unlike an adult patient, whose age is commonly measured in years, a pediatric patient's age can be expressed in days, weeks, months, and years. Patients are classified based on age and may be further described based on other factors, including birth weight and prematurity status (Table 3–1).[1]

Growth and Development

Children are monitored for physical, motor, cognitive, and psychosocial development through clinical recognition of timely milestones during routine well-child visits. As a newborn continues to progress to infant, child, and adolescent stages, different variables are monitored to assess growth compared with the general population of similar age and size. Growth charts are used to plot head circumference, weight, length or stature, weight-for-length, and body mass index for a graphical representation of a child's growth compared with the general pediatric population. These markers of growth and development are both age and gender dependent; thus, the use of the correct tool for measurement is important. For children younger than 2 years, one should use the World Health Organization (WHO) growth standards (Figure 3–1).[2] For children 2 years and older, the Centers for Disease Control and Prevention (CDC) growth charts (Figure 3–2) are used.[3] These tools assess whether a child is meeting the appropriate physical growth milestones, thereby allowing identification of nutritional issues such as poor weight and height gain (eg, failure to thrive).

Differences in Vital Signs

Normal values for heart rate and respiratory rate vary based on age. Normal values for blood pressure vary based on gender and age for all pediatric patients, and also height percentile for patients older than 1 year. Respiratory rates are also higher in neonates and infants (30–60 breaths/min), decreasing with age to adult rates around 15 years of age (12–16 breaths/min).

Normal values for blood pressure in pediatric patients can be found in various national guidelines and other pediatric diagnostic references.[4–7] In general, blood pressure increases with age, with average blood pressures of 70/50 in neonates, increasing throughout childhood to 110/65 in adolescents.[6] Heart rates are highest in neonates and infants, ranging from 85 to 205 beats/min and decrease with age, reaching adult rates (60–100 beats/min) around 10 years of age.

Another vital sign commonly monitored in children by their caregivers is body temperature, especially when they seem "warm to the touch." The American Academy of Pediatrics (AAP) supports the use of rectal measurement of body temperature as it is most accurate when appropriate technique is used; however, for other routes, the AAP offers an age-specific guideline on routes of measurement.[8] For patients aged less than 3 months, axillary temperature is safest for initial measurement, followed by rectal

Table 3–1

Pediatric Age Groups, Age Terminology, and Weight Classification

Age Group	Age
Neonate	≤ 28 days (4 weeks) of life
Infant	29 days to ≤ 12 months
Child	1–12 years
Adolescent	13–17 years (most common definition)
Age Terminology	**Definition**
GA	Age from date of mother's first day of last menstrual period to date of birth
Full term	Describes infants born at 37-week gestation or greater
Premature	Describes infants born before 37-week gestation
Small for GA	Neonates with birth weight below the 10th percentile among neonates of the same GA
Large for GA	Neonates with birth weight above the 90th percentile among neonates of the same GA
Chronological or postnatal age	Age from birth to present, measured in days, weeks, months, or years
Corrected or adjusted age	May be used to describe the age of a premature child up to 3 years of age: Corrected age = Chronological age in months – [(40 – GA at birth in weeks) × 1 month ÷ 4 weeks]. For example, if a former 29-week GA child is now 10 months old chronologically, his corrected age is approximately 7 months: 10 months – [(40 – 29 weeks) × 1 month ÷ 4 weeks] = 7.25 months
Weight Classification	**Definition**
LBW infant	Premature infant with birth weight between 1500 and 2500 g
VLBW infant	Premature infant with birth weight 1000 g to < 1500 g
ELBW infant	Premature infant with birth weight < 1000 g

ELBW, extremely low birth weight; GA, gestational age; LBW, low birth weight; VLBW, very low birth weight.

Based on defined terms in American Academy of Pediatrics, Committee on Fetus and Newborn. Age terminology during the perinatal period. Pediatrics. 2004;114:1362–1364.

measurement if axillary result is above 99°F (37.2°C), for more accurate measurement and determining need for additional medical assessment in case of defined fever. For patients age 3 months to 5 years, oral measurement is reliable with an option to use otic or temporal artery measurement alternatively, after 6 months of age. Axillary measurement is not considered first line in this age group, as proper technique in this age group is important for accurate measurement and other accurate options are available. Generally, fever is defined as temperature 100.4°F (38°C) and greater measured via rectal, otic, or temporal artery technique. For oral and axillary measurement, fever is defined as temperature 100°F (37.8°C) and 99°F (37.2°C) and greater, respectively.[8] Low-grade fevers range from 37.8°C to 39°C (100–102°F), with antipyretic treatment (eg, acetaminophen) considered by most pediatricians in cases of temperature greater than 38.3°C (101°F, any measurement route) accompanied by patient discomfort. Formal definition of fever, like other vital signs, is also age dependent, with a lower temperature threshold for neonates (38°C or 100.4°F) and infants (38.2°C or 100.7°F).[8,9]

Also sometimes considered as the fifth vital sign, pain assessment is more challenging to assess in neonate, infants, and young children due to their inability to communicate symptoms. Indicators of possible pain include physiological changes, such as increased heart rate, respiratory rate, and blood pressure, decreased oxygen saturation, as well as behavior changes such as prolonged, high-pitch crying, and facial expressions.[10] Such indicators are used in validated assessment scales, such as the FACES scale and FLACC (Face, Legs, Activity, Cry, Consolability) scale behavioral tools.[11,12]

Fluid Requirements

Fluid requirement and balance are important to monitor in pediatric patients, especially in premature neonates and infants. Maintenance fluid requirement can be calculated based on body surface area for patients weighing more than 10 kg, with a range of 1500 to 2000 mL/m^2/day. However, a weight-based method of determining normal maintenance fluid requirement for children is often used (Table 3–2).[13]

EFFECTS OF PHARMACOKINETIC AND PHARMACODYNAMIC DIFFERENCES ON DRUG THERAPY

Drug selection strategy may be similar or different depending on age and disease state, as a result of differences in pathophysiology of certain diseases and pharmacokinetic and pharmacodynamic parameters among pediatric and adult patients. It is noteworthy that pediatric patients may require the use of different medications from those used in adults affected by certain diseases. For example, phenobarbital is commonly used for treatment of neonatal seizures but seldom used for seizure treatment in adults, due to differences in seizure etiology and availability of extensive data regarding its use in neonates compared with newer antiepileptic medications. There also exist commonalities between pediatric and adult patients, such as therapeutic serum drug concentrations required to treat certain diseases. For example, gentamicin peak and trough serum concentrations needed for bacteremia treatment are the same in children and adults. Appropriate selection and dosing of drug therapy for a pediatric patient depends on a number of specific factors, such as age, weight, height, disease, comorbidities, developmental pharmacokinetics, and available drug dosage forms. Pediatric drug doses are often calculated based on body weight (eg, mg/kg/dose) compared with uniform dosing (eg, mg/day or mg/dose) for adult patients. Thus, accurate weight should be available while prescribing or dispensing medications

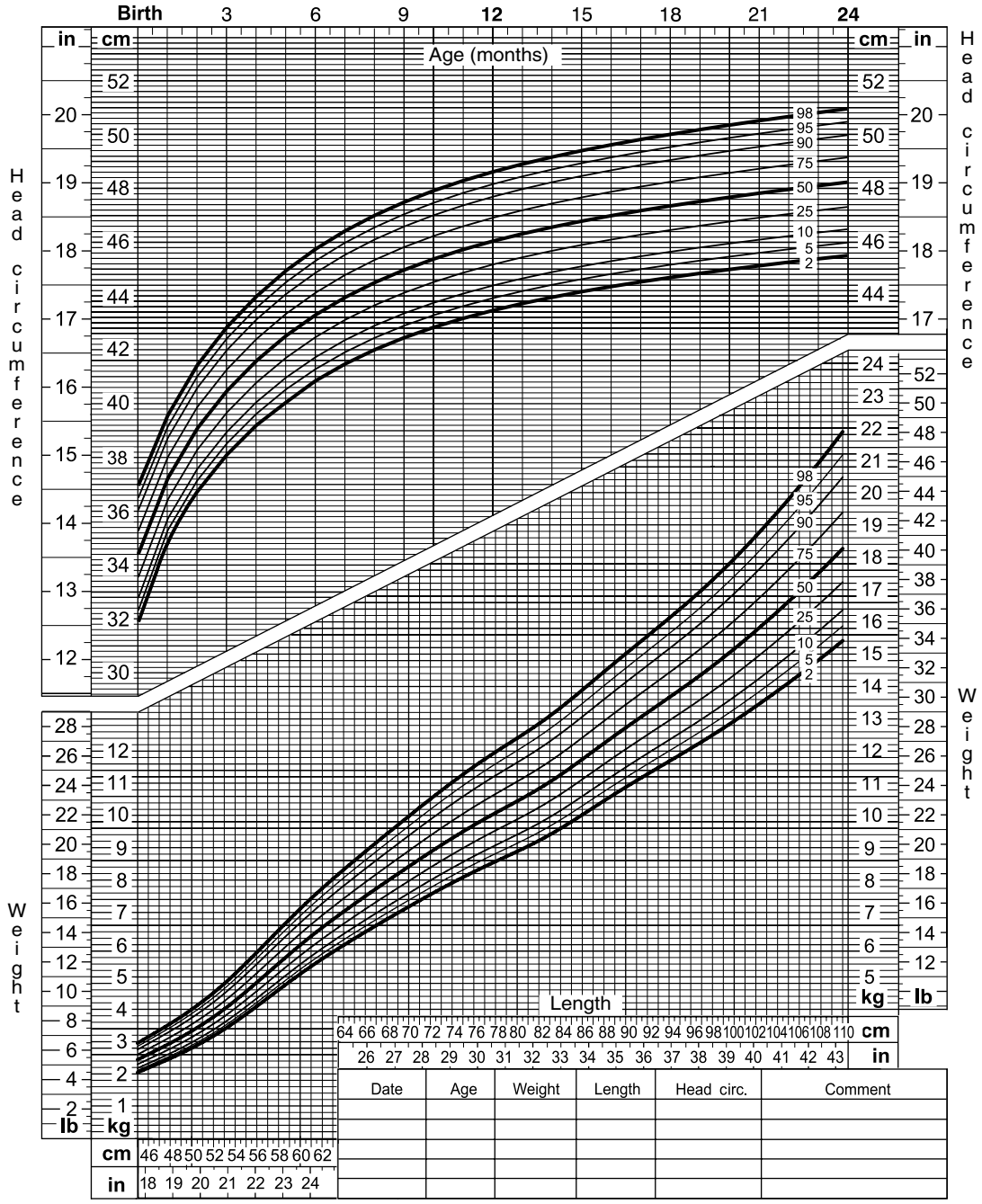

FIGURE 3–1. Example of WHO growth chart of girls, birth to 24 months: Head circumference-for-age and weight-for-length percentile, 2000. (From Centers for Disease Control and Prevention from the WHO Growth Standards. World Health Organization [WHO] Growth Standards, 2009 [updated September 9, 2010], http://www.cdc.gov/growthcharts/who_charts.htm.)

for this patient population. Pediatric doses may exceed adult doses by body weight for certain medications due to differences in pharmacokinetics and pharmacodynamics; hence, the use of pediatric drug dosing guides is recommended.

KEY CONCEPT *Due to multiple differences, including age-dependent development of organ function in pediatric patients, the pharmacokinetics, efficacy, and safety of drugs often differ between pediatric and adult patients; thus, pediatric dosing should not be calculated based on a single factor of difference.* Equations proposed to estimate pediatric doses based on adjusted age or weight, such as the Clark's, Fried's, or Young's rule should not be routinely used to calculate pediatric doses because they account for only one factor of difference (eg, age or weight), and they lack integration of the effect of growth and development on drug pharmacokinetics and pharmacodynamics in this population. For off-label medication dosing, when no alternative treatment is available and limited dosage guidelines have been published, clinicians may estimate a pediatric dose based on body surface area ratio.

Approximate pediatric dose =

Adult dose × [BSA (in m^2) ÷ 1.73 m^2]

Limitations for this dose-estimating approach include the need for the patient to be of normal height and weight for age,

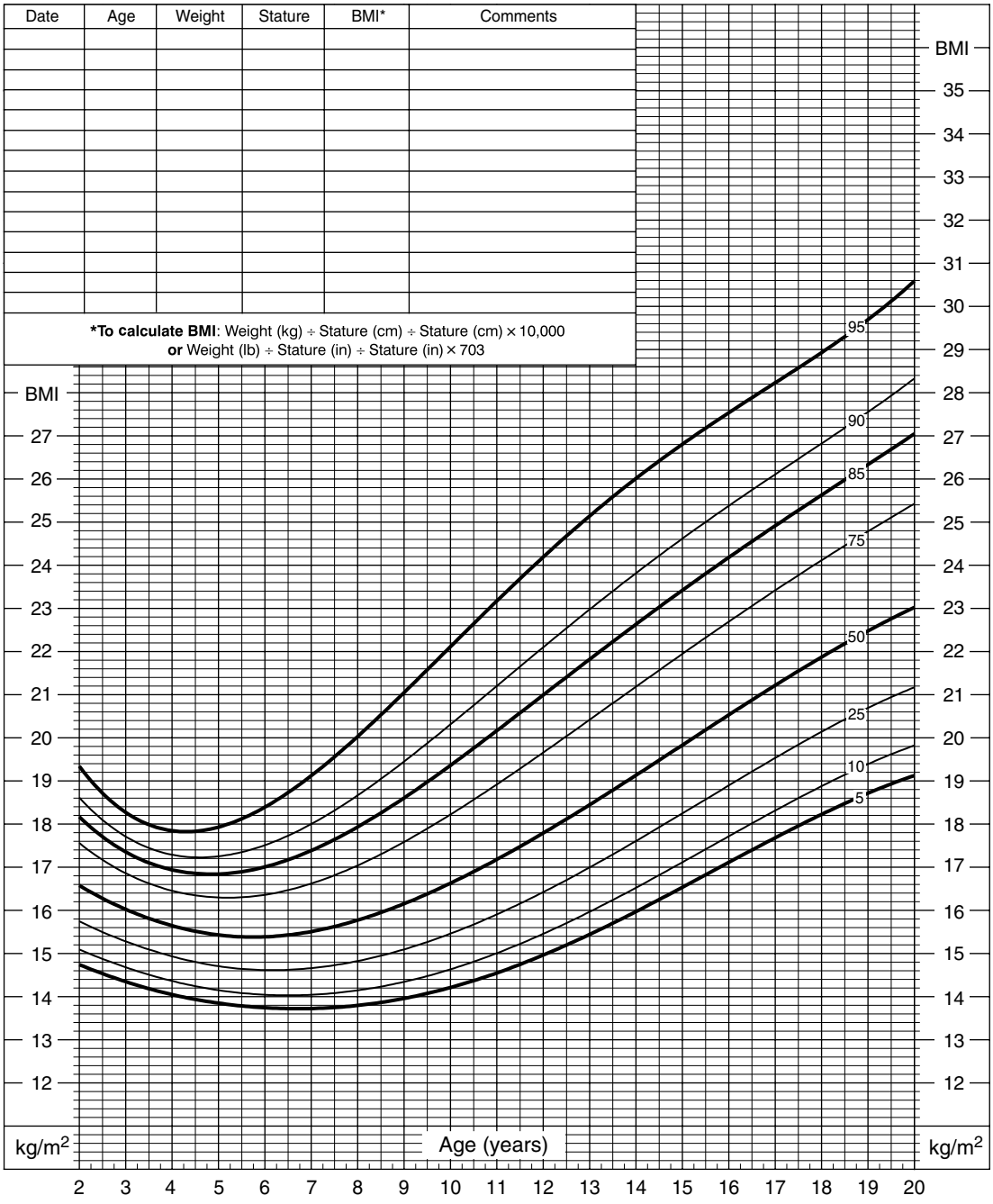

FIGURE 3–2. Example of CDC growth chart of boys, 2 to 20 years: Body mass index for age percentile, 2000. (From National Center for Health Statistics and National Center for Chronic Disease Prevention and Health Promotion. Center for Disease Control Growth Charts, 2000 [updated September 9, 2010], http://www.cdc.gov/growthcharts.)

and lack of incorporation of exact pharmacokinetic differences regarding each medication.[14]

Absorption

Oral absorption may be different in premature infants and neonates due to differences in gastric acid secretion and pancreatic and biliary function. Neonates and infants have increased gastric pH (eg, pH 6–8) due to lower gastric acid output by body weight, reaching adult values by approximately 2 years of age.[15] Low gastric acid secretion can result in increased serum concentrations of weak bases and acid-labile medications, such as penicillin, and decreased serum concentrations of weak acid medications, such as phenobarbital, due to increased ionization. Additionally, gastric emptying time and intestinal transit time are delayed in premature infants, increasing drug contact time with the gastrointestinal mucosa and drug absorption.[15,16] Diseases, such as gastroesophageal reflux, respiratory distress syndrome, and congenital heart disease may further delay gastric emptying time. Pancreatic exocrine and biliary function are also reduced in newborns, with about 50% less secretion of amylase and lipase than adults, reaching adult values as early as the end of the first year and as late as 5 years of age. Deficiency in pancreatic secretions and bile salts in newborns can decrease bioavailability of prodrug esters, such as erythromycin, which requires solubilization or

Table 3–2

Maintenance Fluid Calculations by Body Weight

Patient Body Weight	Maintenance Fluid Requirement
< 10 kg	100 mL/kg/day
11–20 kg	1000 mL + 50 mL/kg over 10 kg
> 20 kg	1500 mL + 20 mL/kg over 20 kg

intraluminal hydrolysis.[15] Due to limited data on oral bioavailability of medications in infants and children for newer agents, some drug dosing recommendations may be extrapolated from adult safety and efficacy studies and case reports.

Topical or percutaneous absorption in neonates and infants is increased due to a thinner stratum corneum, increased cutaneous perfusion, and greater body surface-to-weight ratio. Hence, application of topical medications, such as corticosteroids, should be limited to the smallest amount possible. Limiting exposure can help minimize serum concentrations of active drug as well as inactive, yet potentially harmful additives such as propylene glycol.

Intramuscular absorption in premature and full-term infants can be erratic due to variable perfusion, poor muscle contraction, and decreased muscle mass compared with older patients.[19] Intramuscular administration may be appropriate for some medications; however, use of this route of administration can be painful and is usually reserved when other routes are not accessible, for example, initial IV doses of ampicillin and gentamicin for neonatal sepsis.

Intrapulmonary absorption and disposition is largely due to anatomical size of the lungs and drug delivery. The smaller airways of neonates and lower inspiratory volume can result in greater drug concentrations in the upper and central airways. Particle size, breathing pattern, and route (eg, oral vs nasal) can impact the amount of drug absorbed and should be considered when utilizing pulmonary drug delivery devices such as nebulizers or inhalers.[17]

Rectal absorption can also be erratic due to uncontrollable pulsatile contraction and risk of expulsion in younger patients (ie, infants and young children).[18] Thus, it is not commonly recommended if other routes are available. This route is useful in cases of severe nausea and vomiting or seizure activity. For medications that undergo extensive first-pass metabolism, bioavailability increases as the blood supply bypasses the liver from the lower rectum directly to the inferior vena cava. Availability of rectal dosage forms varies and use of oral medications or other dosage forms rectally is based on limited studies and case reports.

Patient Encounter, Part 1

TS is a 32-week GA premature baby boy weighing 2 kg, length 42 cm, born to a 21-year-old woman this morning.

What is TS's weight classification as a neonate?

Calculate TS's corrected age for TS 8 months from today.

How much maintenance fluid would you recommend for TS at birth?

Volume of Distribution

In pediatric patients, apparent volume of distribution (V_d) is normalized based on body weight and expressed as L/kg. Extracellular fluid and total body water per kilogram of body weight are increased in neonates and infants, resulting in higher V_d for water-soluble drugs, such as aminoglycosides, and decreases with age. Therefore, neonates and infants often require higher doses by weight (mg/kg) than older children and adolescents to achieve the same therapeutic serum concentrations.[15,18] The use of extracorporeal membrane oxygenation (ECMO) can further effect V_d of medications in patients due to the added volume from the circuit and potential fluid changes (eg, edema) while on the circuit. Thus, the use of additional, close clinical and, when available, therapeutic drug monitoring is recommended for those patients requiring ECMO.[19] Neonates and infants have a lower normal range for serum albumin (2–4 g/dL, 20–40 g/L), reaching adult levels after 1 year of age. Highly protein bound drugs, such as sulfamethoxazole-trimethoprim, are not typically used in neonates due to theoretical concern for bilirubin displacement. This displacement may result in a complication known as kernicterus, from bilirubin encephalopathy.[20]

Although neonates have lower body adipose composition compared with older children and adults, their overall V_d for many lipid-soluble drugs (eg, lorazepam) is similar to infants and adults. Some medications (eg, vancomycin, phenobarbital) may also reach higher concentrations in the central nervous system of neonates due to an immature blood-brain barrier.[18]

Metabolism

Hepatic drug metabolism is slower at birth in full-term infants compared with adolescents and adults, with further delay in premature neonates. Phase 1 reactions and enzymes, such as oxidation and alcohol dehydrogenase, are impaired in premature neonates and infants and do not fully develop until later childhood or adolescence. Accordingly, the use of products containing ethanol or propylene glycol can result in increased toxicities, including respiratory depression, hyperosmolarity, metabolic acidosis, and seizures, thus should be avoided in neonates and infants. Age at which cytochrome P450 isoenzymes (eg, CYP3A4, CYP2C19) activity reaches adult values varies, depending on the isoenzyme, with delayed development in premature infants. Increased dose requirements by body weight (eg, mg/kg) for some hepatically metabolized medications (eg, phenytoin, valproic acid) in young children (ie, ages 2–4 years) is theorized due to an increased liver mass to body mass ratio.[21] This increase in metabolism slows to adult levels as the child goes through puberty into adulthood.[15,21]

Among phase 2 reactions, sulfate conjugation by sulfotransferases is well developed at birth in term infants. Glucuronidation by the uridine diphosphate glucuronosyltransferases, in contrast, is immature in neonates and infants, reaching adult values at 2 to 4 years of age.[15,21] In neonates, this deficiency results in adverse effects including cyanosis, ash gray color of the skin, limp body tone, and hypotension, also known as "gray baby syndrome" with use of chloramphenicol.[22] Products containing benzyl alcohol or benzoic acid should be avoided in neonates due to immature glycine conjugation, resulting in accumulation of benzoic acid. This accumulation can lead to "gasping syndrome," which includes respiratory depression, metabolic acidosis, hypotension, seizures or convulsions, and gasping respirations.[23] Acetylation via *N*-acetyltransferase reaches adult maturation at around 1 year of life; however, overall activity is dependent on genotypic variability.[15]

Elimination

Nephrogenesis completes at approximately 36-week gestation; thus, premature neonates and infants have compromised glomerular and tubular function that may correlate with a glomerular filtration rate (GFR). This reduction in GFR affects renal drug clearance; thereby necessitating longer dosing intervals for renally cleared medications, such as vancomycin, to prevent accumulation. GFR increases with age and exceeds adult values in early childhood, after which there is a gradual decline to approximate adult value during adolescence. For example, vancomycin is often given every 18 to 24 hours in a low birth weight (LBW) premature neonate, every 6 hours in children with normal renal function, and every 8 to 12 hours in adult patients with normal renal function. Children with cystic fibrosis also present with greater renal clearance of drugs such as aminoglycosides, compared with children without the disease, requiring higher doses by weight and more frequent dosing intervals.[24]

Pediatric GFR, also referred to as "creatinine clearance," informally by clinicians, is normalized due to variable body size (mL/min/1.73 m^2). The Cockroft–Gault, Jelliffe, or modification of diet in renal disease (MDRD) equations for estimating GFR in adults should not be used for evaluating patients younger than 18 years.[25,26] The Schwartz equation is a common method of estimating pediatric GFR from infancy up to 21 years of age (Figure 3–3). This equation uses patient length (cm), serum creatinine (mg/dL) (or µmol/L × 0.0113), and a constant, *k*, which depends on age (including LBW status for infants) for all patients and also gender for those older than 12 years.[27] There is also a simplified version of this equation, validated for ages 1 to 16 years old, commonly referred to as the "bedside" Schwartz equation.[28]

Estimated GFR = [0.413 × height (in cm)] ÷ serum creatinine (in mg/dL)

Or

Estimated GFR = [36.5 × height (in cm)] ÷ serum creatinine (in µmol/L)

$$GFR = \frac{kL}{SCr}$$

Age	k
Low birth weight < 1 year	0.33
Full term < 1 year	0.45
1–12 year	0.55
13–21 year (female)	0.55
13–21 year (male)	0.70

k = Proportionality constant

L = Length in cm

SCr = Serum creatinine in mg/dL

GFR = estimated glomerular filtration rate (i.e., creatinine clearance) in mL/min/1.73 m^2

FIGURE 3–3. Schwartz equation for estimation of glomerular filtration rate (GFR) in pediatric patients up to 21 years of age. (Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. Pediatr Clin North Am. 1987;34(3):571–590.)

Patient Encounter, Part 2

TS is now 8 weeks old (weight: 3.5 kg) and presents to the community pharmacy with a 3-day history of lethargy, poor oral intake, and low-grade fever. The pharmacist refers the child to seek medical attention at the emergency department. TS is admitted to the general pediatric ward for further assessment including a neonatal sepsis and meningitis rule-out. Blood samples, cerebral spinal fluid, and urine were collected for Gram stain and culture, still pending results. He was empirically started on ampicillin 175 mg (50 mg/kg/dose) IV q 6 h, cefuroxime 175 mg IV q 6 h (50 mg/kg/dose). Given his poor oral intake on admission, the team requests addition of maintenance IV fluids and a nutrition consultation.

BB's Laboratory Values	Normal Ranges
WBC 18 × 10^3/mm^3 (18 × 10^9/L)	6–17 × 10^3/mm^3 (6–17 × 10^9/L)
Bands 7% (0.07)	4%–12% (0.04–0.12)
Segs 36% (0.36)	13%–33% (0.13–0.33)
Lymphs 51% (0.51)	41%–71% (0.41–0.71)
Monocytes 6% (0.06)	4%–7% (0.04–0.07)

Serum creatinine 0.5 mg/dL (44 µmol/L) ≤ 0.6 mg/dL (53 µmol/L)

How much maintenance fluid would you recommend for TS now?

The team decides to change cefotaxime to gentamicin (ie, meningitis ruled out). Because gentamicin can affect renal function, TS's GFR should be assessed. Using the most appropriate method, calculate an estimated GFR for TS.

Because serum creatinine is a crude marker of GFR, the Schwartz equation, as with other estimation calculations, carries limitations including the potential for overestimating GFR in patients with moderate to severe renal insufficiency.[29,30] Urine output is also a parameter used to assess renal function in pediatric patients, with a urine output more than 1 to 2 mL/kg/hour considered normal.

SPECIFIC CONSIDERATIONS IN DRUG THERAPY

In addition to differences in pharmacokinetics and pharmacodynamic parameters, other factors, including dosage formulations, medication administration techniques, and parent/caregiver education, should be considered when selecting drug therapy.

Off-Label Medication Use

Currently, there is a lack of pediatric dosing, safety, and efficacy information for more than 75% of drugs approved in adults.[31] Off-label use of medications occur in both outpatient and inpatient settings. Off-label use of medication is the use of a drug outside of its approved labeled indication. This includes the use of a medication in the treatment of illnesses not listed on the manufacturer's package insert, use outside the licensed age range, dosing outside those recommended, or use of a different route of administration.[32,33] KEY CONCEPT *It is appropriate to use a drug off-label when no alternatives are available; however,*

clinicians should refer to published studies and case reports for available safety, efficacy, and dosing information. FDA regulatory changes, such as extended patent exclusivity, provide incentives for a pharmaceutical manufacturer to market new drugs for pediatric patients. However, such incentives are not available for generic drugs.

Routes of Administration and Drug Formulations

Depending on age, disease, and disease severity, different routes of administration may be considered. The rectal route of administration is reserved for cases where oral administration is not possible and IV route is not necessary. Topical administration is often used for treatment of dermatologic ailments. Transdermal routes are often not recommended, unless it is an approved indication such as the methylphenidate transdermal patch for treatment of attention deficit hyperactivity disorder. The injectable route of administration is used in patients with severe illnesses or when other routes of administration are not possible. As done with adult patients, IV compatibility and access should be evaluated when giving parenteral medications. Dilution of parenteral medications may be necessary to measure smaller doses for neonates. However, a higher concentration of parenteral medications may be necessary for patients with fluid restrictions, such as premature infants and patients with cardiac anomalies and/or renal disease. Appropriate stability and diluent selection data should be obtained from the literature.

When oral drug therapy is needed, one must also consider the dosage form availability and child's ability to swallow a solid dosage form. Children younger than 6 years are often not able to swallow oral tablets or capsules and may require oral liquid formulations. Not all oral medications, especially those unapproved for use in infants and children, have a commercially available liquid dosage form. Use of a liquid formulation compounded from a solid oral dosage form is an option when data are available. Factors such as drug stability, suspendability, dose uniformity, and palatability should be considered when compounding a liquid formulation.[34] Commonly used **suspending agents** include methylcellulose and carboxymethylcellulose (eg, Ora-Plus). Palatability of a liquid formulation can be enhanced by using simple syrup or Ora-Sweet. If no dietary contraindications or interactions exist, doses can be mixed with food items such as pudding, fruit-flavored gelatin, chocolate syrup, applesauce, or other fruit puree immediately before administration of individual doses. Honey, although capable of masking unpleasant taste of medication, may contain spores of *Clostridium botulinum* and should not be given to infants younger than 1 year due to increased risk for developing botulism. Most hospitals caring for pediatric patients compound formulations in their inpatient pharmacy. Limited accessibility to compounded oral liquids in community pharmacies poses a greater challenge. A list of community pharmacies with compounding capabilities should be maintained and provided to the parents and caregivers before discharge from the hospital.

Common Errors in Pediatric Drug Therapy

Prevention of errors in pediatric drug therapy begins with identification of possible sources. The error rate for medications is as high as 1 in 6.4 orders among hospitalized pediatric patients.[35] Off-label use of medications increases risk of medication error and has been attributed to difference in frequency of errors compared with adults. One of the most common reasons for medication errors in this specialized population is incorrect dosing such as calculation error.[36,37] KEY CONCEPT *Medication errors among pediatric patients are possible due to differences in dose calculation and preparation; it is important to identify potential errors through careful review of orders, calculations, dispensing, and administration of drug therapy to infants and children.* It is crucial to verify accurate weight, height, and age for dosing calculations and dispensing of prescriptions because pediatric patients are a vulnerable population for medication error. Consistent units of measurements in reporting patient variables, such as weight (kg) and height (cm), should be used. Dosing units such as mg/kg, mcg/kg, mEq/kg, mmol/kg, or units/kg should also be used accurately. Given the age-related differences in metabolism of additives, such as propylene glycol and benzyl alcohol, careful consideration should be given to the active and inactive ingredients when selecting a formulation.

Decimal errors, including trailing zeroes (eg, 1.0 mg misread as 10 mg) and missing leading zeroes (eg, .5 mg misread as 5 mg) in drug dosing or body weight documentation are possible, resulting in several-fold overdosing. Strength or concentration of drug should also be clearly communicated by the clinician in prescription orders. Similarly, labels that look alike may lead to drug therapy errors (eg, mistaking a vial of heparin for insulin). Dosing errors of combination drug products can be prevented by using the right component for dose calculation (eg, dose of sulfamethoxazole/trimethoprim is calculated based on the trimethoprim component).

Use of standardized concentrations and programmable infusion pumps, such as smart pumps with built-in libraries, is encouraged to minimize errors with parenteral medications, especially those for continuous infusions such as inotropes. Computer physician order entry (CPOE) systems and bar coding technology, with ability for dose range checks by weight for pediatric medication orders and accurate matching of correct ordered medication to patient, respectively, have decreased medication errors.[37]

Prevention of medication errors is a joint effort between health care professionals, patients, and parents/caregivers. Obtaining a complete medication history, including over-the-counter (OTC) and complementary and alternative medicines (CAMs), simplification of medication regimen, clinician awareness for potential errors, and appropriate patient/parent/caregiver education on measurement and administration of medications, are essential in preventing medication errors.

Complementary and Over-the-Counter Medication Use

Between 30% and 70% of children with a chronic illnesses (eg, asthma, attention deficit hyperactivity disorder, autism, cancer) or disability use CAMs.[38] CAMs can include mind-body therapy (eg, imagery, hypnosis), energy field therapies (eg, acupuncture, acupressure), massage, antioxidants (eg, vitamins C and E), herbs (eg, St. John's wort, kava, ginger, valerian), prayer, immune modulators (eg, echinacea), or other folk/home remedies. It is important to encourage communication about CAM use, including interdisciplinary discussion between CAM providers and pediatric health care providers.[38] It is critical to appreciate that there are limited data establishing efficacy of various CAM therapies in children. For example, colic is a condition of unclear etiology in which an infant cries inconsolably for over a few hours in a 24-hour period, usually during the same time of day. Symptoms of excessive crying usually improve by the third month of life and often resolve by 9 months of age. No medication has been approved by the FDA for this condition. Some parents are advised by family and friends to use alternative treatments, such as gripe water, to treat colic. Gripe water is an oral solution

containing a combination of ingredients, such as chamomile and sodium bicarbonate, not regulated by the FDA. In addition, some gripe water products may contain alcohol, which is not recommended for infants due to their limited metabolism ability (ie, alcohol dehydrogenase). Further, some CAM products (eg, St. John's wort) can interact with prescription drugs and produce undesired outcomes. It is important to assess OTC product use in pediatric patients. For example, treatment of the common cold in children is similar to adults, including symptom control with adequate fluid intake, rest, use of saline nasal spray, and acetaminophen (10–15 mg/kg/dose every 6–8 hours) or ibuprofen (4–10 mg/kg/dose every 8 hours) for relief of discomfort and fever. Other products, such as a topical vapor rub or oral honey, have demonstrated some potential for alleviation of symptoms, such as cough, based on survey studies of parents for children of 2 years and older.[39,40] Unlike adults, symptomatic relief through the use of pharmacologic agents, such as OTC combination cold remedies, is not recommended for pediatric patients younger than 4 years. Currently, the FDA does not recommend the use of OTC cough and cold medications (eg, diphenhydramine and dextromethorphan) in children younger than 2 years; however, the Consumer Healthcare Products Association, with the support of the FDA, has voluntarily changed product labeling of OTC cough and cold medications to state "do not use in children under 4 years of age." This is due to increased risk for adverse effects (eg, excessive sedation, respiratory depression) and no documented benefit in relieving symptoms. It has also been noted that these medications may be less effective in children younger than 6 years compared with older children and adults.[41,42] Also noteworthy is the potential for medication error with use of OTC products in older children, such as cold medications containing diphenhydramine and acetaminophen. A parent/caregiver may inadvertently overdose a child on one active ingredient, such as acetaminophen, by administering acetaminophen suspension for fever and an acetaminophen-containing combination product for cold symptoms. The use of aspirin in patients younger than 18 years with viral infections is not recommended due to the risk of Reye syndrome. While making an appropriate recommendation for an OTC product for a pediatric patient, the parent/caregiver should always be referred to their pediatrician for further advice and evaluation when severity of illness is a concern.

Clinicians should respect parents'/caregivers' beliefs in the use of CAM and OTC products and encourage open discussion with the intention of providing information regarding their risks and benefits to achieve desired health outcomes as well as optimize medication safety.

Medication Administration to Pediatric Patients and Caregiver Education

Considering the challenges in cooperation from infants and younger children, medication administration can become a difficult task for any parent or caregiver. One should also consider factors that may affect adherence to prescribed therapy including caregiver and/or patient's personal beliefs, socioeconomic limitation(s), and fear of adverse drug effects. One common factor to consider is ease of measurement and administration when selecting and dosing pediatric drug therapy. Clinicians should check concentrations of available products and round doses to a measurable amount. For example, if a patient were to receive an oral formulation, such as amoxicillin 400 mg/5 mL suspension, and the dose was calculated to be 4.9 mL, the dose should be rounded to 5 mL for ease of administration. Rounding the dose by 10% to the closest easily measurable amount is commonly practiced for most medications (eg, antibiotics); however, drugs with narrow therapeutic indices (eg, anticoagulants) are exceptions to this guideline.

The means or devices for measuring and administering medications should also be closely considered. Special measuring devices as well as clear and complete education about their use are essential. Oral syringes are accurate and offered at most community pharmacies for the measurement of oral liquid medications. Oral droppers included specifically with a medication may be appropriate for use in infants and young children. Medicine cups are not recommended for measuring doses for infants and young children due to the possible inaccuracy of measuring smaller doses. Household dining or measuring spoons are not accurate or consistent and should not be used for the administration of oral liquids.

KEY CONCEPT *Comprehensive and clear parent/caregiver education improves medication adherence, safety, and therapeutic outcomes and is essential in care of infants and young children.* Information about the drug, including appropriate and safe storage away from children, possible drug interactions, duration of therapy, importance of adherence, possible adverse effects, and expected therapeutic outcomes should be provided. Parent/caregiver education is important in both inpatient and outpatient care settings and should be reviewed at each point of care.

Because parents/caregivers are often sole providers of home care for ill children, it is important to demonstrate appropriate dose preparation and administration techniques to the caregivers before medication dispensing. First, a child should be calm for successful dose administration. Yet, calming a child is often a challenge during many methods of administration (eg, otic, ophthalmic, rectal). Parents/caregivers should explain the process in a simple and understandable form to the child because this may decrease the child's potential anxiety. In addition, it is also recommended to distract younger children using a favorite item such as toy or to reward cooperative or "good" behavior during medication administration. Helpful tips regarding administration of selected dosage forms in pediatric patients are listed in Table 3–3.[43]

Accidental Ingestion in Pediatric Patients

Pediatric accidental ingestions most often occur in the home.[44] Various factors account for incidence of accidental ingestions in young children, including hand-to-mouth behaviors as well as new and increased mobility resulting in easier access areas where

Patient Encounter, Part 3

TS is now 18 months old, and his mother calls the clinic and tells you that her son is "just miserable" with a runny nose, cough, and a fever (axillary temperature) of 37.8°C (100°F). She wanted to know if she could use baby aspirin instead of the acetaminophen that does not seem to help. She also wanted to know which cough and cold preparation would be most appropriate for TS.

What additional information would you need to help TS and his mom?

What is your recommendation regarding use of aspirin for TS's fever?

What would you recommend for TS's cold symptoms?