SIXTH EDITION

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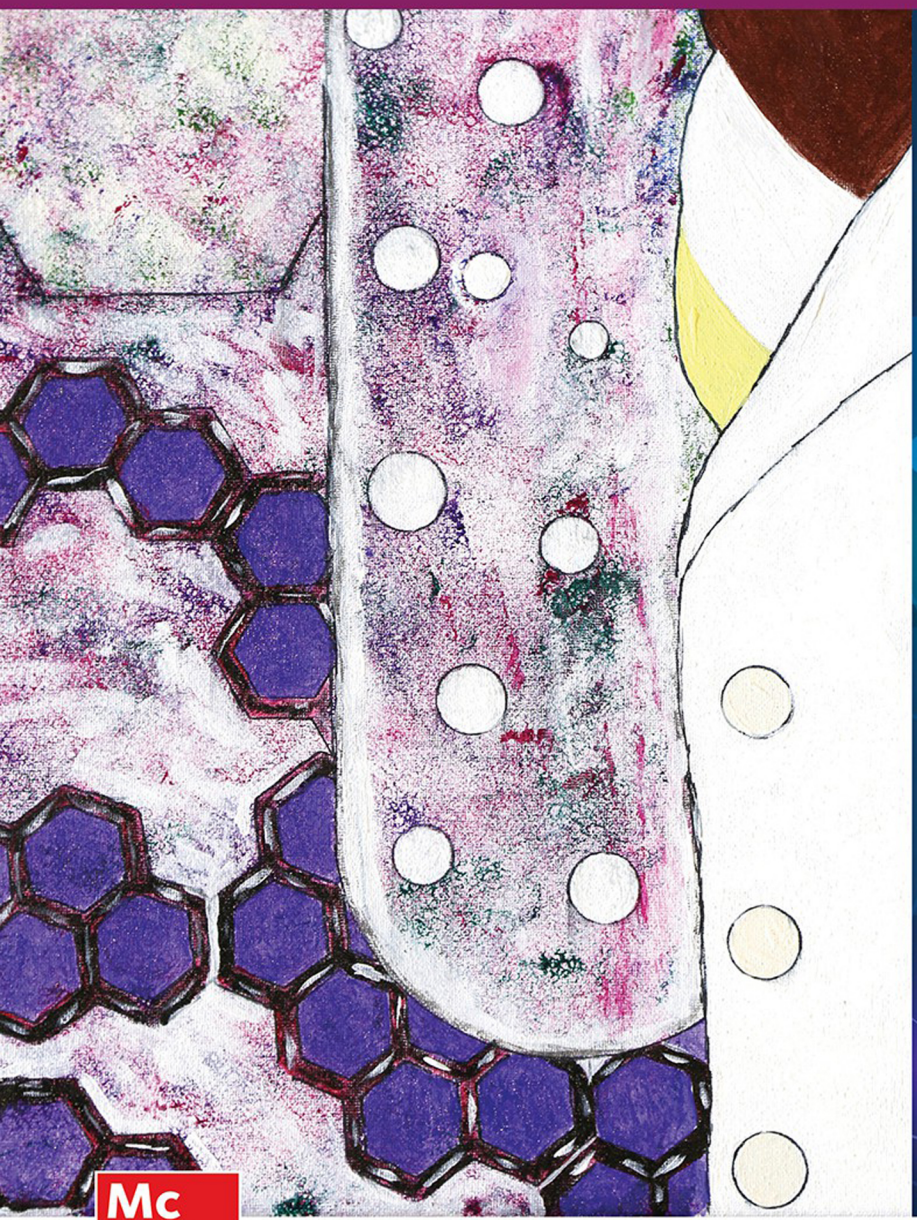

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Pharmacotherapy Principles & Practice

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Pharmacotherapy Principles & Practice

SIXTH EDITION

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The editors dedicate this edition to our families for their support
and express immense gratitude to healthcare workers around the world.

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CONTENTS

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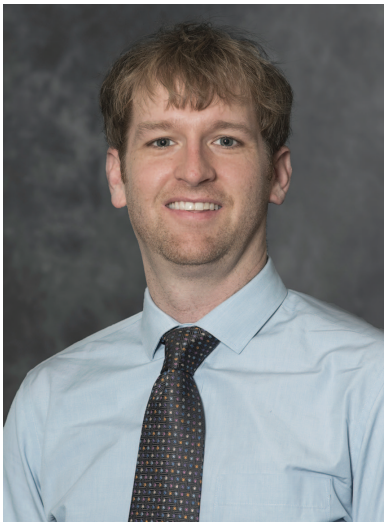

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PREFACE

Safe and effective use of pharmacotherapy is critical for preventing and treating acute and chronic medical conditions. Although biomedical research continues to lead to production of medications with great potential to improve health, medications are often overused, underused, or misused, leading to suboptimal or unsafe results. As healthcare practitioners, we are responsible for optimizing positive health outcomes and limiting adverse effects from pharmacotherapy.

Providing high quality, cost-effective pharmacotherapy requires integration of scientific knowledge and clinical practice skills combined with patient-centered care. The development of healthcare practitioners occurs through structured educational processes that include didactic and experiential learning, independent study, mentorship, interprofessional experiences, and direct involvement in patient care.

The sixth edition of *Pharmacotherapy Principles & Practice* is designed to provide student learners and healthcare practitioners with essential knowledge of the pathophysiology and pharmacotherapy of acute and chronic diseases likely to be encountered in routine practice. Chapters are written by content experts and peer reviewed by pharmacists, nurse practitioners, physician assistants, and physicians who are authorities in their professional disciplines.

Pharmacotherapy Principles & Practice, sixth edition, opens with a brief Introduction chapter followed by five chapters focused on special populations: pediatrics, geriatrics, palliative care, critical care, and global health and travel medicine. These chapters are followed by 97 disease-based chapters that review epidemiology, etiology, pathophysiology, clinical presentation and diagnosis, and nonpharmacologic therapy, followed by an emphasis on clear recommendations for medication selection, desired outcomes, dosing, and patient monitoring. New chapters in this edition include critical care pharmacotherapy; global health and travel medicine; systemic lupus erythematosus; and nose, mouth, and throat disorders. There is also important new chapter content on circulatory shock syndromes, trauma-related anxiety disorder, otic disorders, and antimicrobial stewardship.The following textbook features were designed in collaboration with educational design specialists to enhance learning and retention:

- *Structured learning objectives* at the beginning of each chapter.
- *Key concepts related to the disease, patient assessment,* and *treatment* highlighted with an easily identifiable icon throughout the chapter.
- *Patient encounters*, updated and revised from the previous edition, that facilitate development of critical thinking skills and lend clinical relevance to the scientific foundation provided.
- A *patient care process* section modeling the Joint Commission of Pharmacy Practitioners (JCPP) that provides specific recommendations about the process of care for an individual patient involving five steps: collect information, assess information, develop a care plan, implement the care plan, and follow-up: monitor and evaluate.
- *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 healthcare 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 website, *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 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.

We are extremely grateful for the commitment and dedication of more than 190 contributing authors and more than 100 peer reviewers of the chapters in this new edition. We also thank the many educators, schools/colleges, and healthcare institutions that have adopted this textbook in courses or use it as a reference in practice settings. We extend our sincere thanks to the McGraw Hill team for their hard work and commitment to bringing this new edition to our readership.

The Editors
September 2021

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INTRODUCTION

Jack E. Fincham

INTRODUCTION

Health professionals are given significant responsibilities in our healthcare 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 positive 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 healthcare system from a structural standpoint. In 2018, the United States spent twice as much as comparative countries on health care, yet the United States ranks 11th in the list that considers increased hospitalization from preventable causes and an increase in avoidable deaths.[1] Keehan and colleagues[2] from the US Centers for Medicare and Medicaid Services (CMS) projected the costs of health care through 2028 and estimate that by 2028, US healthcare expenditures will exceed $6.2 trillion with prescription drug spending estimated to be $560.3 billion. This prescription drug spending amounts to a projected increase in spending of 74% between 2016 and 2028.

A significant issue in the United States is that countless Americans in our midst are uninsured or 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 each time they seek care or pay premiums. The Coronavirus Disease (COVID-19) pandemic has amplified the lack of health insurance for many in this country.[3] The swelling of the ranks of the unemployed also means many with prior health insurance through an employer are now not only out of work but also without health insurance. In addition, many other social determinants of care impact who receives health care or not.

The use of medications in the healthcare system provides enormous benefit to many; lives are saved or enhanced, and lifespans 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 healthcare 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.

The following are issues that will impact you as you develop as a healthcare professional or impact your patients as they use medications. These are important issues to consider as you enhance your knowledge concerning medications and how they can impact your patients.

CORONOVIRUS DISEASE 2019 (COVID-19)

The COVID-19 pandemic has wreaked havoc globally upon economic, social, and health structures. Healthcare practitioners have been stressed as never before. Driggin and colleagues[4] have written of the risks heathcare workers are exposed to when providing cardiovascular care and become hosts or vectors of COVID-19 transmission. Much has been written of the fear healthcare workers are experiencing since they fear for their coworkers, their family and friends, and their communities.[5,6] Rose[7] has noted the rapid change of teaching techniques from traditional pre-clerkship course delivery to online learning applications that are now required for health professional curricula during this pandemic.

The general public has experienced significant detrimental emotional impacts due to the COVID-19 pandemic. Pfefferbaum and North[8] have written of the trauma, including post-traumatic stress disorders (PTSD), patients are experiencing due to concerns related to their health, safety, well-being, economic status, and stress disorders. You will have an enormous opportunity to positively impact patients and families in your practices.

DRUG USE IN THE HEALTHCARE SYSTEM

Prescription medications are used daily and 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 healthcare institutions, and elsewhere. Herbal remedies and countless cannabidiol (CBD) products are marketed and sold in numerous outlets. The monitoring of the 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 (e.g., allergies and dermatologic conditions), if appropriately treated through patient self-medication, allow the patient to have a degree of autonomy in healthcare decisions.

Non-Adherence Issues

Non-adherence is not taking a prescribed medication or not taking it as prescribed and is one of the most understated problems in the healthcare system.[9] Reasons can include not being able to get the medication in a timely manner because of insurance requirements such as a prior approval from the insurance being denied or delayed, the prescribed drug may not be covered under the patient's insurance, the patient cannot afford to pay the drug cost or the copay, regimens are complicated or not understood by the patient, etc. The effects of non-adherence have enormous ramifications for patients, caregivers, and health professionals. Non-adherence 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 adherence rates and subsequent positive health outcomes.

Drug Use by the Elderly

The major source of payment for prescription drugs for those age 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 $88 billion in 2020.[10]

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.

IMPACTING THE PROBLEMS OF DRUG USE

Medication Errors

There is a tremendous opportunity in medication use and monitoring to reduce medication errors. Untold morbidity and mortality occur due to the many errors occurring in medication use. The increasing availability of artificial intelligence applications, and increased usage by healthcare professionals can enhance the proper provision of patient care for all patients.[11]

Avoiding Prescribing Cascades

Prescribing cascades occur in healthcare when the side effect from a medication is interpreted as a new condition—and a second drug is prescribed to "treat" the side effect. Prescribing cascades are important because they can be prevented.[12]

Impacting the Opioid Crisis

The use and misuse of prescription opioid analgesic medications are at an all-time high and are increasing, and the negative consequences of this epidemic are many.[13] Health professionals will play a key, vital role in reversing this epidemic and enhancing the health of many and society as well.

SUMMARY

Health professionals are at a crucial juncture facing an uncertain, yet promising future. 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. Continuing healthcare reforms will have the potential to dramatically impact your practices in the healthcare system for the length of your careers.

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.

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Part I

Special Populations

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1 Geriatrics: Safe Medication Use in Older Adults

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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 healthcare professionals to gain knowledge necessary to meet the needs of this patient group. Despite the availability and benefit of numerous pharmacotherapies, older patients commonly experience drug-related problems, resulting in additional morbidities. Therefore, it is essential for clinicians serving older adults across all healthcare settings to understand the epidemiology of aging, age-related physiological changes, drug-related problems prevalent in elders, comprehensive geriatric assessment, and interprofessional approaches to care.

EPIDEMIOLOGY AND ETIOLOGY

As humans age, they are at increasing risk of disease, disability, and death for three reasons: genetic predisposition; reduced immunological surveillance; and the accumulated effects of physical, social, environmental, and behavioral exposures over the life course. Elders experience variably increasing vulnerability (**homeostenosis**) as they age, resulting in 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 clinicians to better understand the epidemiology of aging to comprehensively provide high-value services to optimize the function and health-related quality of life of older adults.[1]

Sociodemographics

▶ *Population*

KEY CONCEPT The population is rapidly growing older. In 2020, 56.1 million US residents were 65 years and older, with projections to increase to 94.7 million by 2060.[2] Almost 6.7 million people were 85 years or older (the "oldest-old"), and 100 thousand persons were aged 100 or older.[2] Those 85+ years individuals are projected to grow from 6.4 million in 2016 to 14.4 million in 2040 and further increase to 19 million by 2060.[2] In 2020, older women aged 65 years and above (31 million) outnumbered older men (25 million), with a ratio of 100 to 81; this ratio widens as elders age.[2] Additionally, minority elders are projected to increase to 21.1 million in 2020.[3] With changing aging population demographics, surviving baby boomers will be disproportionally female, more ethnically/racially diverse, better educated, live alone, and have more financial resources than elders in previous generations.

▶ *Economics*

More elders have higher economic prosperity than ever before. In 2017 only 9.2% of Americans of 65 years and older and 11.6% of 80 years and older lived below the poverty line.[4] However, major inequalities persist, with older Blacks (poverty rates of 16.1% for men and 21.5% for women) and those without high school diplomas reporting fewer financial resources.[4,5] Considerable disparities exist and may prevent less advantaged elders from purchasing 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.[6] Nearly 40% of people 75+ years have low **health literacy**, more than any other age group.[5] Despite these limitations, the Pew Trust reports that 67% of adults aged 65 years and older say they use the Internet,[7] and healthcare systems are increasingly offering online health information to older consumers. These advances are important because communication between healthcare providers and elders is vital in providing quality care, supporting self-care, and navigating care transitions.

Health Status

▶ *Life Expectancy*

Americans are living longer than ever (average of 78.6 years in 2017), and life expectancy has increased (people who survive to age 65 can expect to live an average of 19.3 more years).[5] Yet, US life expectancy lags behind that of many other industrialized nations.[5,8] Disparities in mortality persist; in 2014 life expectancy at birth for the Whites was 3.4 years longer than for the Blacks.[5]

Nearly 35% of US deaths in 2000 were attributed to three risk behaviors: smoking, poor diet, and physical inactivity. Though only 8.4% of Americans 65+ years smoked in 2018, nearly 54% of men and 21% of women were former smokers.[5,9] Overweight elders aged 65 to 74 years increased from 57% to 73% in 2004, largely due to inactivity and a diet high in refined foods, saturated fats, and sugared beverages.[5] Despite proven health benefits of physical activity, 47% of elders 65 to 74 years and 61% of 75+ years reported no physical activity, and only 12% of older adults reported participating in aerobic and muscle-strengthening activities that meet US physical activity guidelines.[5,10]

The 2016 National Health Interview Survey indicated that in 2012 to 2014 older non-Hispanic Whites were more likely to report good to excellent health than non-Hispanic Blacks and Hispanic peers (80% vs 65% and 66%, respectively).[11] Approximately 85% of older adults have at least one chronic condition, and 60% 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%).[8] Figure 1–1 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. Among US adults 65 years and older, 15.3% were frail according to the National Health and Aging Trends Study.[12]

Healthcare Utilization and Cost

KEY CONCEPT Older Americans use more healthcare services than younger Americans do. Although older adults with one or more hospital stays decreased from 2000 to 2017 (18% vs 15.3%), they accounted for more than half of hospitalizations overall, with longer lengths of stay corresponding to increasing age.[8] Between 2015 and 2016, there were 1.2 million US nursing home residents aged 65+ years, and as the aged live longer, more will require assistance, which will be increasingly performed in the home.[8]

Healthcare costs among older Americans are higher than costs for younger Americans. In 2015 older Americans spent 12.9% of their total expenditures on health compared with 7.8% among all consumers.[3] Medicare plays a major role in US healthcare costs, accounting for 20% of total health spending in 2012, 27% of spending on hospital care and 23% on physician services.[13]

Patient Encounter Part 1

CS is an 85-year-old widow who moved to California with her sister 10 years ago to be near their children at the end of life. Though CS has a college degree in art in Japan, she speaks very little English, has limited health literacy, and requires interpretation during health visits. CS comes to the Interprofessional Geriatrics Clinic to receive comprehensive care of her multimorbidity and polypharmacy management. Her past medical history includes depression, diabetes, dyslipidemia, hypertension, hypothyroidism, insomnia, myocardial infarction (14 years ago), and peripheral neuropathy. CS uses 19 medications that include prescription medications for her multiple chronic conditions, vitamins, and herbal supplements for "immune system and sleep." She is underweight, despite eating often to maintain her weight. She walks around her neighborhood with her sister for about 30 minutes every morning, then drinks three to four cups (about 0.75–1 L) of tea while listening to Japanese news.

What information is consistent with epidemiology of aging?

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

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

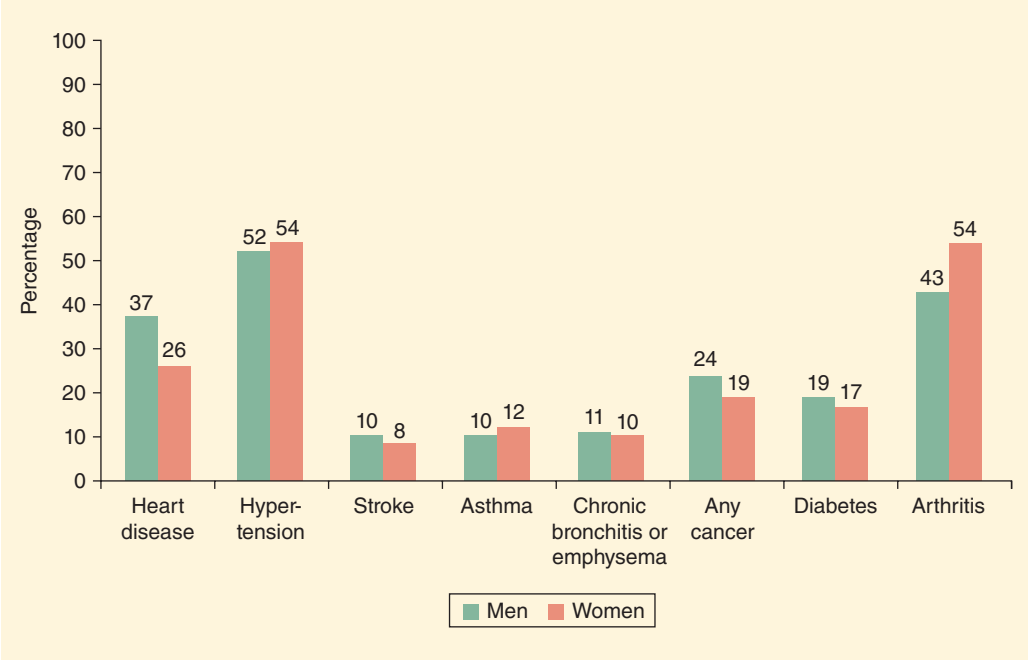


FIGURE 1–1. Percentage of people 65 years and older who reported having selected chronic conditions, by sex, 2005 to 2006. Note: Data are based on a 2-year average from 2005 to 2006. Reference population: These data refer to the noninstitutionalized population. (From Centers for Disease Control and Prevention,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

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.[14] As people age, they can become frailer and are more likely to experience altered and variable drug pharmacokinetics and pharmacodynamics. Even though this change is influenced by a patient's clinical state more than their chronological age, the older patient is more likely to be malnourished or suffer from diseases that affect pharmacokinetics and pharmacodynamics.[14] Older adults can develop significant drug-related problems when alterations in pharmacokinetics and pharmacodynamics are not appropriately accounted for in prescribing and monitoring medications.[13] Clinicians have the responsibility to use pharmacokinetic and pharmacodynamic principles to improve elder care and avoid adverse effects of pharmacotherapy. Due to the many changes described below, certain chronic medications should be started at 50% of the recommended initial adult dose with doses titrated slowly in older adults. This is a general recommendation for initiating medications, such as antihypertensives and antidepressants, but does not apply to the treatment of acute illness (eg, antibiotics for pneumonia).

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.[14] Peristalsis becomes weaker, and gastric emptying is 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.[14,15] However, relative **achlorhydria** can decrease the absorption of nutrients, such as vitamin B_{12}, calcium, and iron.[15]

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 older adults due to unpredictable drug absorption.[14] Additionally, because saliva production decreases with age, medications that need to be absorbed rapidly by the buccal mucosa are absorbed at a slower rate. Yet, for most drugs, absorption is not significantly affected, and the changes described are clinically inconsequential.[15,16]

▶ *Distribution*

The main physiological changes that affect distribution of drugs in older adults are with body fat and water and protein binding. Lean body mass can decrease by 12% to 19% through loss of skeletal muscle in older adults. Thus, blood levels of drugs primarily distributed in muscle increase (eg, digoxin), presenting a risk for overdose.[15] 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, amitriptyline, and amiodarone) 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.[14,15]

Total body water decreases by 10% to 15% by age 80. This lowers V_d of water-soluble drugs (eg, aspirin, digoxin, and morphine) leading to higher plasma drug concentrations than in younger adults when equal doses are used.[14,15] Thus lower doses are needed to prevent toxicity. Toxic drug effects may be worsened 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.[14] In patients with an acute illness, rapid decreases in serum albumin can increase drug effects. Examples of highly protein-bound medications include warfarin, phenytoin, and diazepam.[15] For most chronic medications, these changes are not clinically significant because although the changes affect peak level of a single dose, mean serum concentrations at steady state are not altered unless clearance is affected.[15] 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.[14] Hence, if a hypoalbuminemic patient has a low total phenytoin level, and phenytoin dose is increased, the free phenytoin concentration may reach toxicity.

▶ *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.[14,16] Liver mass is reduced by 20% to 30% with aging, and hepatic blood flow is decreased by as much as 50%.[15] 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.[15] Metabolic clearance of some drugs is decreased by 20% to 40% (eg, amiodarone, amitriptyline, and morphine), but it is unchanged for drugs with a low hepatic extraction.[15] 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 are seen with propranolol, levodopa, calcium channel blockers, tricyclic antidepressants, and statins. Thus, older patients may respond similarly to younger patients using lower doses of these medications.[14-16]

Aging affects liver enzymes (cytochrome P450 system [CYP450]) that may lead to a decreased elimination rate of drugs that undergo oxidative phase I metabolism, but this is controversial.[14] Originally, it was thought that the CYP450 system was impaired in older adults, leading to decreased drug clearance and increased serum half-life, but studies have not consistently confirmed this. The variations in the CYP450 activity may not be due to aging but lifestyle (eg, smoking), illness, or drug interactions.[14-16] Nutritional status also plays a role in drug metabolism. Frail elders have a more diminished drug metabolism than those with healthy body weight.[14,16] Aging does not affect drugs that undergo phase II hepatic metabolism (eg, lorazepam and temazepam), known as conjugation or glucuronidation, but conjugation is reduced with frailty.[15]

▶ *Elimination*

Clinically, the most important pharmacokinetic change in older adults is decreased renal drug elimination.[14] As people age, renal blood flow, renal mass, glomerular filtration rate, filtration fraction, and tubular secretion decrease. After age 40, the number of functional glomeruli declines, and renal blood flow decreases 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.[14,15] Still, the impact of age on renal function is variable and not always linear. Longitudinal studies have suggested that a percentage (up to 33%) of older adults do not experience this age-related decline in renal function.[15] Clinically significant effects of decreased renal clearance include prolonged drug half-life, increased serum drug level, and increased potential for **adverse drug reactions (ADRs)**.[14] Special attention should be given to renally eliminated drugs with a narrow therapeutic index (eg, digoxin and aminoglycosides). Monitoring serum concentration and making appropriate dose adjustment for these agents can prevent serious ADRs resulting from drug accumulation.[17] Importantly, 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 frail older patients have decreased muscle mass resulting in less creatinine production for input into circulation.[14,15] Because chronic kidney disease can be overlooked if a clinician focuses only on the serum creatinine value, overdose and ADR can occur.

Creatinine clearance should be calculated when starting or adjusting pharmacotherapy in older adults. The Cockcroft-Gault equation is the most widely used formula for estimating creatinine clearance (mL/min; or multiply by 0.0167 to express in mL/s) for adjusting drug doses. See Chapter 26 (Table 26–3) for more details.

When serum creatinine is expressed in mg/dL,

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

When serum creatinine is expressed in μmol/L,

$$\text{Creatinine Clearance} = 1.2 \times \frac{(140 - \text{Age}) \times \text{Weight (kg)}}{\text{Serum creatinine (μmol/L)}} \times (0.85 \text{ if female})$$

This equation is also used by most drug manufacturers to determine renal dosing guidelines. The Cockcroft-Gault equation provided the best balance between predictive ability and bias in a comparison study with the Modification of Diet in Renal Disease (MDRD) and Jelliffe "bedside" clearance equations.[15] The Cockcroft-Gault equation can overestimate renal function in obese individuals, so an adjusted body weight should be used in the calculation [AjBW = IBW + 0.4 (ABW − IBW)]. Understand that predictive formulas can also 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. Compared to pharmacokinetics, there is less data on age-related pharmacodynamic changes. KEY CONCEPT In general, the pharmacodynamic changes that occur in older adults tend to increase their sensitivity to drug effects. Most pharmacodynamic changes in elders are associated with a progressive reduction in homeostatic mechanisms and changes in receptor properties. Although the result of these changes is an increased sensitivity to the effects of many drugs, a decrease in response can also occur. The changes in the receptor site include alterations in binding affinity of the drug, number/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.[14,15]

▶ *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 decreased arterial compliance and baroreceptor reflex response, which limits the ability to compensate quickly for postural changes in blood pressure. It has been estimated that 5% to 33% of older adults experience drug-induced orthostasis. Examples, other than typical antihypertensives, that can cause orthostatic hypotension in older patients are antipsychotics, direct vasodilators, loop diuretics, and opioids.[14,15,17] Older people have a decreased β-adrenergic receptor function, and they are less sensitive to β-agonist and β-adrenergic antagonist effects in the cardiovascular system and possibly in the lungs, but their response to α-agonists and antagonists is unchanged.[14,15] Increased hypotensive and heart rate response (to a lesser degree) to calcium channel blockers (eg, verapamil) are reported. Increased risks of developing drug-induced QT prolongation and **torsade de pointes** are also present.[17] Therefore, clinicians must start medications at low doses and titrate slowly, closely monitoring the patient for any adverse effects.

▶ *Central Nervous System*

Overall, elders exhibit a greater sensitivity to the effects of drugs that gain access to the central nervous system (CNS), especially anticholinergic medications. 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.[14,15] The blood–brain barrier becomes more permeable as people age; more medications can cross the barrier and cause CNS effects. Examples include benzodiazepines, antidepressants, antipsychotics, neuroleptics, and antihistamines. There are decreased numbers of cholinergic neurons as well as nicotinic and muscarinic receptors, decreased choline uptake from the periphery, and increased acetylcholinesterase.[14,15] Older adults have a decreased ability to compensate for these imbalances of the neurotransmitters, leading 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).[14,15]

▶ *Fluids and Electrolytes*

Fluid and electrolyte homeostatic mechanism is decreased in elders. Older adults 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.[17] The result is increased incidences 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.[14] Thus, these agents need to be started with low doses, titrated slowly with frequent renal function monitoring.

▶ *Glucose Metabolism*

An inverse relationship between glucose tolerance and age has been reported, likely due to reduced insulin secretion and sensitivity (greater insulin resistance). Consequently, hypoglycemia incidences are increased when using sulfonylureas (eg, glyburide, glipizide) from age-related impairment to counter-regulate hypoglycemic responses.[14] Due to an impaired autonomic nervous system, older patients may not distinguish symptoms of hypoglycemia such as sweating, palpitations, or tremors. They still experience neurological symptoms of syncope, ataxia, confusion, or seizures.

DRUG-RELATED PROBLEMS

KEY CONCEPT Comorbidities and polypharmacy complicate health status of older adults, particularly inappropriate medications that lead to drug-related problems. It is estimated that 43.6% of emergency department visits leading to hospitalizations in older adults are due to adverse drug events.[18] Studies indicated that 59% of the older Medicare beneficiaries' sample had at least one medication-related problem, and drug-related morbidity and mortality costed US healthcare system $528.4 billion in 2016.[19,20] Drug-related problems result in poor health outcomes for older adults such as withdrawal effects, therapeutic failure, and adverse drug events.[21] Collaboration among interprofessional providers and older patients can ensure appropriate therapy, minimize adverse drug events, and maximize medication adherence and health outcomes.

Polypharmacy

Polypharmacy is defined as taking multiple medications concurrently (≥ 4–10 medications have been used as criteria in studies). Polypharmacy is prevalent among elders with 39% reporting the use of five or more medications in 2012 compared with polypharmacy use by 24% in 1999, signifying a dramatic increase.[22] In 2011, 67% of older adults used polypharmacy including nonprescription products, an increase from 53% in 2006.[18] The common use of dietary supplements and herbal products in this population adds to polypharmacy. In nursing home settings 50.7% of patients with severe cognitive impairment received polypharmacy (5–9 medications), and 16.9% received excessive polypharmacy (≥ 10 medications).[23] Among various reasons for polypharmacy, an apparent one is an older patient receiving multiple medications from different providers who treat the patient's comorbidities without coordinated care. Hence, medication reconciliation becomes increasingly important as the aging population continues to grow.

A complete evaluation of all medications should be conducted by healthcare providers at each elder's visit to prevent inappropriate polypharmacy. 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 multimorbidity, 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. Potentially inappropriate medications in older adults have been associated with negative outcomes such as confusion, falls, and mortality.[24] 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's use of over-the-counter (OTC) agents and herbal supplements.[21]

Screening tools have been developed to help the clinician identify potentially inappropriate medications in older adults. The most utilized tool in the US is the Beers criteria.[24] The 2019 Beers criteria includes 30 medications and medication classes that are potentially inappropriate in older patients, listed in five categories: medications potentially inappropriate in most older adults, medications that should typically be avoided in older adults with certain conditions, medications to use with caution, drug–drug interactions, and drug dose adjustment based on kidney function.[24]

Examples of medications included in the Beers criteria are as follows[24]:

- Benzodiazepines such as diazepam and alprazolam (risk of cognitive impairment, delirium, falls, fractures, and motor vehicle accidents)
- First-generation antihistamines such as diphenhydramine and hydroxyzine (risk of confusion, dry mouth, constipation, and other anticholinergic symptoms)
- Tricyclic antidepressants (TCAs) such as amitriptyline and nortriptyline (risk of sedation, orthostatic hypotension, and anticholinergic symptoms)
- Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen (risk of GI bleeding and ulcers)

Practical strategies for appropriate medication prescribing include establishing a partnership with patients and their care partners to enable them to understand and monitor medication effects. Clinicians should perform a comprehensive medication assessment to obtain accurate history of medication use, determine appropriateness of the regimen, conduct drug–drug and drug–disease interaction screenings, use time-limited trials to evaluate the benefits and risks of new medications, and trial off medications to assess continued need.[21]

Undertreatment

Much has been written about the consequences of overmedication and polypharmacy in older adults. 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.[21,25] Undertreatment is prevalent across diverse settings in the community, hospitals, and long-term care facilities.[21] Many reasons include multimorbidity, polypharmacy, cost, concerns of nonadherence, fear of adverse effects and associated liability, limited evidence in the age group, starting low and failing to increase to an appropriate dose, skepticism regarding secondary prevention benefits, or ageism.[21,26] Common categories of geriatric undertreatment are listed in Table 1–1.

Table 1–1

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	Hesitant to prescribe opioids due to possible cognitive and bowel side effects, concerns about addiction; patients may often be hesitant to use 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 goals and preferences, prognosis or life expectancy, and time to therapeutic benefit should be taken into consideration to determine whether pharmacotherapy meets treatment goals. Underprescribing can best be avoided by using clinical assessment strategies, improving adherence support, and assisting 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. ADRs increase with polypharmacy use and are the most frequently occurring drug-related problem among older nursing home residents. A brown bag medication review study found that 25% of community-dwelling older adults using at least five medications experienced ADRs.[27] Approximately 9% of hospitalizations among older adults are caused by ADRs.[28] Medication classes causing serious ADRs in older adults include anticoagulants, antidiabetics, and opioids.[29]

Seven predictors of ADRs in elders are[30] taking more than four medications; more than 14-day hospital stay; having more than four active medical problems; general medical unit admission versus geriatric ward; alcohol use history; lower Mini-Mental State Examination score (confusion, dementia); and two to four new medications added during a hospitalization. Similarly, four predictors of severe ADRs in older adults are[31] use of certain medications including diuretics, NSAIDs, antiplatelets, and digoxin; number of drugs taken; age; and comorbidities. Suggested strategies to prevent ADRs in older adults are described in Table 1–2.[31] Particular caution must be taken when prescribing drugs that alter cognition in older adults, including antidepressants, antihistamines, antipsychotics, benzodiazepines, opioids, and muscle relaxants.[31]

One of the most damaging ADRs that frequently occurs in elders is medication-related falls. Falls are associated with a poor prognosis ranging from premature institutionalization to early death, and polypharmacy is a risk factor. Multiple medications included in the Beers criteria are related to falls.[24] For example, benzodiazepine studies found significant association with falls including an increased risk after a new prescription for benzodiazepines and twofold risk with combined use of two or more benzodiazepines.[32] Other agents having strong association with increased fall risk include sedative hypnotics, neuroleptics, antidepressants, and antipsychotics.[32] A comprehensive fall prevention intervention should include deprescribing by slow taper with close monitoring.

Table 1–2

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, Charmes JP. Predicting and preventing adverse drug reactions in the very old. Drugs Aging. 2005;22(5):375–392.

Nonadherence

America's other drug problem is the term given to medication nonadherence by the National Council on Patient Information and Education. Nonadherence to chronic medications is prevalent and escalates healthcare costs associated with worsening disease and increased hospitalization. *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 healthcare provider.[33]

KEY CONCEPT Older adults are at greater risk for medication nonadherence due to the high prevalence of multimorbidities, cognitive deficit, polypharmacy use, and financial barriers. Numerous barriers to optimal 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.[33] Factors influencing nonadherence are listed in Table 1–3.

Following is a list of six "how" questions to ask when assessing medication adherence[34]:

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 medicines?

Table 1–3

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

Although no single intervention has found to improve adherence consistently, older person-centered multicomponent interventions, such as combining education, adherence aid, and regular follow-up, have resulted in a positive impact on medication adherence and associated health outcomes.[35] Future research needs include adherence studies evaluating belief-related variables, such as personal and cultural beliefs, in larger and more ethnically/racially diverse samples of older populations.

Patient Encounter Part 2

CS was recently hospitalized after an episode of dizziness and near-fall. Her daughter (interpreter) states that there were several medication changes while CS was in the hospital with some confusion as to what to do at home. CS brought in all medication bottles used at home: (1) amlodipine 10 mg by mouth every morning, (2) aspirin 81 mg by mouth every morning, (3) calcium-vitamin D 600 mg-500 units by mouth every morning and evening, (4) eszopiclone 2 mg by mouth at bedtime, (5) gabapentin 900 mg by mouth three times a day, (6) hydrochlorothiazide 50 mg by mouth every morning, (7) levothyroxine 50 mcg by mouth in the morning, (8) melatonin 3 mg by mouth at bedtime, (9) metformin 500 mg morning and evening, (10) omeprazole 40 mg by mouth every morning, (11) rosuvastatin 5 mg by mouth every evening, (12) valsartan 40 mg by mouth every morning and evening, (13) vitamin B_6 200 mg by mouth every morning and evening, (14) vitamin C 5000 mg by mouth every morning and evening, (15) vitamin E 400 units by mouth every morning and evening, (16) acetaminophen 500 mg two tablets by mouth every 4 hours as needed for pain, (17) ibuprofen 200 mg by mouth three times a day as needed for headaches, (18) pantoprazole 20 mg by mouth in the morning as needed for stomach upset, (19) valerian root 1200 mg by mouth at night as needed for sleep.
She is allergic to sulfa drugs (rash) and intolerant to ramipril (cough).
She does not smoke, has one or two drinks a night, does not use any illicit drug.
VS: BP 122/64 mm Hg, P: 70 beats/min, RR: 12, T: 37.2°C (99°F)
Ht: 5 ft (152 cm), Wt: 42 kg, Pain 1/10
Labs: Na 139 mEq/L (mmol/L), K 4.1 mEq/L (mmol/L), Cl 98 mEq/L (mmol/L), CO_2 25 mEq/L (mmol/L), BUN 22 mg/dL (7.9 mmol/L), creatinine 1.5 mg/dL (133 µmol/L), glucose 97 mg/dL (5.4 mmol/L), $HgbA_{1c}$ 6.5% (0.065; 48 mmol/mol Hgb), eGFR 35.1 mL/min/1.73 m^2

What is CS's estimated creatinine clearance?

What drug-related problems are included in CS's medication list?

What steps should be taken to simplify CS's medication regimen?

Patient Encounter Part 3

CS is now 91 years old and has been living at a long-term care facility for a year. She still struggles to maintain her weight, is in pain daily, and has developed a new coccyx ulcer. She is currently on multiple medications including (1) amitriptyline 10 mg by mouth at bedtime, (2) aspirin 81 mg by mouth daily, (3) docusate sodium 100 mg by mouth twice daily, (4) hydrochlorothiazide 25 mg by mouth daily, (5) ibuprofen 600 mg by mouth daily, (6) levothyroxine 25 mcg by mouth daily, (7) lorazepam 1 mg by mouth twice daily, (8) metformin 500 mg by mouth daily, (9) rosuvastatin 5 mg by mouth every evening, (10) vitamin C 500 mg by mouth twice daily, (11) valsartan 40 mg by mouth twice daily.
Today her pain score is 8/10.

Which quality indicators should be of concern in CS?

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

GERIATRIC ASSESSMENT

The term *geriatric assessment* is used to describe the comprehensive interprofessional team evaluation of the frail or complex older adult's health including multimorbidity with functional and cognitive status. 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 various care settings and by a series of evaluations after which the team will conduct an interprofessional case conference to discuss the patient's care 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.[36] Functional status must be determined, including the activities of daily living (ADLs) and instrumental activities of daily living (IADLs), see Table 1–4. Cognitive assessment, which may require collateral history from family or care partners, is important in determining the patient's capacity to manage their medications and consent to medical treatment.[37] The mini-cog mental status examination[38] shown in Figure 1–2, is a quick tool to assess patient's cognition. Elders commonly have decreased visual acuity, hearing loss, dysphagia, and impaired dexterity. Decreased skin integrity greatly increases risk for pressure ulcers. Sexual function is a sensitive but important topic and should be specifically addressed. 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 1–5 for common problems experienced by older adults.

It is important to recognize geriatric syndromes such as cognitive decline, functional impairment, polypharmacy, delirium, frailty, falls, osteoporosis, insomnia, and incontinence. In elders, common diseases may present with atypical symptoms, such as thyroid dysfunction or infection presenting as delirium. It is also important to assess for caregiver stress and be aware of older

Table 1–4

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		

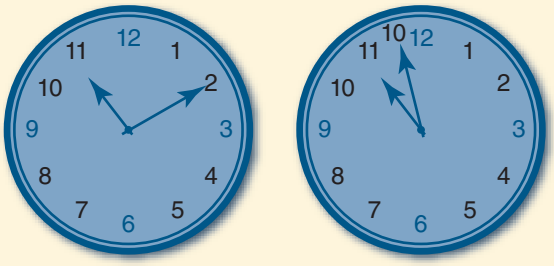
ADL, activity of daily living; IADL, instrumental activity of daily living.

Three item recall

1. Ask the patient if you may test his or her memory.
2. Give the patient 3 words (eg. apple, table, penny) to repeat and remember.
3. Have the patient repeat the 3 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 3 words.
2. Failure to remember 1–2 words plus an abnormal clock drawing.

FIGURE 1–2. 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 1–5

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	

From Hajjar ER, Hersh LR, Gray SL. Prescribing in the older adult. In: DiPiro JT, Yee GC, Posey L, Haines ST, Nolin TD, Ellingrod V, eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw-Hill; 2020. Available from: https://accesspharmacy.mhmedical.com/content.aspx?bookid=2577&sectionid=233054609. Accessed September 1, 2020.

patients' support systems that may include family, friends, social or religious networks, home health agencies, and hired caregivers. Such networks may facilitate older individuals to continue living independently. Safety should be assessed and includes a home safety assessment and a driving assessment for patients with cognitive or functional limitations. In addition, look for signs and symptoms of elder abuse, neglect, or exploitation. Health professionals are mandatory reporters of elder mistreatment to Adult Protective Services.[39]

Drug Therapy Monitoring

Geriatric patients often have multiple medications, comorbidities, and prescribers. It is essential that there be a single provider who oversees the patient's pharmacotherapy. Particularly challenging in elders is identifying the cause(s) of medication 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 medications.[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?

Regarding cost, 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, formulary, and nonformulary drugs? Is the patient responsible for all drug costs during the Medicare "donut hole" period? (In basic part D plans, patients pay increasing percentages of drug costs up to $7425 per year.[40]) 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.[41] Providers can assist patients by prescribing generic medications that are offered through community pharmacy discount plans ($4 retail pharmacy programs do not bill insurance, thus are not counted toward their Medicare part D deductible) and help patients apply for the medication assistance programs offered by drug manufacturers.

Documentation

A clear, current, and accurate medication list must be available to the patient and all individuals involved in their care. It is particularly important for older adults to bring medication containers for reconciliation by a clinician. Medication adherence may require verification with the pharmacist, caregivers, or family. Transitions in care, such as hospital to subacute nursing facility or home, lead to medication errors because medications may have been deleted or added.[42] It is standard of care to conduct medication reconciliation upon hospital admission and discharge to ensure that the medication list is up to date.

Patient Education

Geriatric patients often have difficulty understanding and retaining provider instructions. "Ask me 3" cues the patient to ask three important questions of their providers to improve health literacy[43]:

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 Addressing deficits in vision, hearing, swallowing, cognition, motor impairment, and health literacy can lead to enhanced medication adherence. Specific drug formulations, such as inhalers, ophthalmic/otic drops, nasal sprays, and subcutaneous injections, will require detailed education and practice. Patients who cannot swallow tablets/capsules need instructions on which tablets are safe to crush and which capsules safe to open and sprinkle on food. Patients and/or caregivers need to be advised of potential ADRs and when to notify the provider.

GERIATRIC PRACTICE SITES

Some say geriatrics has become a nonspecialty due to the aging population. Clinicians with geriatric certification or training practice in nearly all settings of healthcare, primary care to wide spectrums of specialty care and long-term care. A few interprofessional practice sites are highlighted here. See Chapter e3 for information on palliative care practices.

Ambulatory Care Clinic and Home-Based Primary Care

Geriatric clinics are established to provide a multitude of primary care needs specifically tailored to older adults. Home-based primary care is delivered in the home or independent living facility of homebound patients to facilitate independent living. Patients are usually referred by their primary care providers to increase access to services, meet complex care needs due to multimorbidity and polypharmacy, and offer a comprehensive geriatric assessment. It is common for the onset of cognitive impairment to be the catalyst for a referral to geriatric services. Interprofessional team care is the norm in these settings, which benefits patients with multifaceted needs. The interprofessional teams hold regular meetings to discuss care plans of involved patients. Geriatricians, who specialize in elder care, assess and treat physical, medical, emotional, and social needs. Nurses provide medical triage and day-to-day patient care activities such as obtaining vitals, providing wound care, educating and ensuring adherence. Clinical pharmacists focus on medication regimen optimization, evidence-based disease state management, drug-related problem resolution, and patient, caregiver, and healthcare team education about pharmacotherapy and monitoring parameters. Social workers address social and structural needs, in addition to assessing mood and cognitive status, facilitating completion of advance directives and obtaining placement in higher levels of care. Physical/occupational therapists work to improve the patient's functional status, provide fall prevention interventions, and maintain a safe home environment. They provide adaptive equipment such as grab bars, raised toilet seats and shower benches for the bathroom, and cane/walker for ambulation. Dieticians evaluate the patient's nutritional status and educate on proper diet and weight management. Using these team collaborations, specialty settings have been developed including a multidisciplinary geriatric oncology clinic[44] and PACE centers (Programs of All-inclusive Care for the Elderly) that incorporate the interdisciplinary team and adult day healthcare in one center.[45]

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 65+ years in 2008.[46] 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.[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 under long-term care insurance coverage.[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 the following problem areas[48]:

- Use of more than nine medications in a 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

Long-term care practices emphasize the interprofessional team approach. The medical director leads regular meetings with care providers. The pharmacist conducts a monthly drug review of

Patient Care Process

1. Collect Information:

- Perform a comprehensive medication reconciliation and review.
- Have the patient bring all medication bottles, including prescriptions, OTC agents, vitamins, supplements, and herbal products.
- Review medical history and physical assessment.
- Ask about allergies/intolerance.
- Inquire about ADRs (Table 1–2).
- Collect adherence information using combination of methods (eg, self-report, refill history, dosage form count, demonstration of nonoral agent use).
- Ask about prevention including vaccinations.
- Collect vital signs and laboratory results.
- Inquire about functional status (Table 1–4).
- Measure cognitive status (Figure 1–2).

2. Assess the Information:

- Identify indication(s) for all medications.
- Assess for potential inappropriate medications using Beers criteria.[24]
- Assess medication doses to determine underdose/overdose.
- Screen for drug–drug/disease/supplement/herbal/food interactions.
- Check against allergies/intolerance.
- Identify ADRs.
- Assess medication adherence (Table 1–3).
- Identify untreated indication/undertreatment (Table 1–1).
- Evaluate vital signs, including pain, and laboratory.
- Assess medication needs based on cognitive and functional status.
- Recognize common problems in older adults (Table 1–5).

3. Develop a Care Plan:

- Discontinue unnecessary medications.
- Tailor regimen: simplify dosing frequency, modify time of dosing based on ADRs and drug interactions, and tie medication taking to individuals' daily routine to improve adherence.
- Develop educational materials, keeping in mind health literacy and cognitive status.
- Create solutions to any functional barriers (eg, non–child-resistant caps, tablet cutters).
- Draft referral plan to target nonpharmacological strategies (eg, diet, physical therapy, behavioral health, integrative health approaches).

4. Implement the Care Plan:

- Educate about medications and disease states in health literacy-sensitive manner.
- Highlight any medication changes and tailored regimen.
- Educate on the use of nonoral agents (eg, inhalers, insulin, ophthalmic/otic drops).
- Provide a medication chart/list to include generic/brand names, indication, dose, directions for use, timing of dose, etc.
- Teach about medication storage, expiration date, and refill status.
- Emphasize adherence and what to do when a dose is missed/forgotten.
- Use medication organizers (eg, pillbox, blister pack) or other adherence aids (eg, alarm, phone reminder) when indicated.
- Implement solutions to any physical/functional barriers (eg, non-childproof caps).
- Refer for nonpharmacological interventions.

5. Follow-up: Monitor and Evaluate:

- Provide a list of future appointments and follow-up.
- Promote self-monitoring (eg, recognize and report ADRs, use blood pressure monitor or glucometer).
- Encourage therapeutic lifestyle modifications including diet, exercise, and smoking cessation.
- Endorse prevention including immunizations, wellness visits, eye examinations, and dental care.
- Formulate a patient-centered and interprofessional team-based follow-up plan to track patient response, adverse events, adherence, and health outcomes.

each patient's medication list.[46] 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.

CONCLUSION

By applying the principles of geriatrics, clinicians can better intervene with pharmacotherapy to postpone disease, disability, and mortality, and promote health, functioning, and health-related quality of life. In addition, interprofessional geriatric care improves health outcomes.

List of Abbreviations

ADL	Activities of daily living
ADR	Adverse drug reaction
GABA	γ-Aminobutyric acid
$HgbA_{1c}$	Hemoglobin A_{1c}
IADL	Instrumental activities of daily living
LDL-C	Low-density lipoprotein-cholesterol
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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2 Pediatrics Pharmacotherapy

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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. Identify factors that affect selection of safe and effective drug therapy in pediatric patients.
3. Explain general pharmacokinetic and pharmacodynamic differences in pediatric versus adult patients.
4. Develop strategies for appropriate and effective medication administration to infants and young children.
5. Determine approaches to effectively communicate with patients and caregivers about appropriate medication use including expected outcomes, possible adverse effects, and appropriate administration.

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 regard 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 2–1).[1–3]

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's (WHO) growth standards (Figure 2–1).[4] For children 2 years and older, the Centers for Disease Control and Prevention (CDC) Growth Charts (Figure 2–2) are used.[5,6] 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). Failure to thrive is defined as inadequate physical growth with weight that falls below the fifth percentile or decreases over time, crossing two or more major percentile lines. Body habitus is often evaluated at routine checkups or well-check visits, with definitions of underweight as body mass index (BMI) less than the 5th percentile for age, overweight as BMI between 85th to 94th percentile for age, and obese as BMI greater than 95th percentile.[7] Since these charts were developed based on a general, healthy population, growth charts may not be accurate evaluation of physical development in children with congenital diseases. Growth charts specific to disease states (eg, Turner syndrome or cystic fibrosis) with regard to expected growth trajectory and/or nutritional goals may be utilized by clinicians as part of care.

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 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 (12–20 breaths/min).[8–10] (Table 2–2).

Normal values for blood pressure in pediatric patients are found in various national guidelines and other pediatric diagnostic references. In general, blood pressure increases with age, with average blood pressures of approximately 70/50 in neonates, increasing throughout childhood to approximately

Table 2–1

Pediatric Age Groups, Age Terminology, and Weight Classification[1-3]

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-weeks' gestation or greater
Premature	Describes infants born before 37-weeks' 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.

110/65 in adolescents.[8,9] Heart rates are highest in neonates and infants, ranging from 90 to 205 beats/min and decrease with age, reaching adult rates (60–100 beats/min) around 10 years of age.[8-10]

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.[11,12] For patients younger than 3 months, rectal measurement using a digital thermometer is recommended. For those 3 months and older, use of temporal artery is an available option. The use of tympanic measurement is appropriate for patients who are 6 months and older. Axillary measurement is not considered first-line in all these age groups, as proper technique is important for accurate measurement, and other accurate options are available. For patients age 4 or 5 years and older, oral measurement is reliable. 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.[12] Low-grade fevers range from 100° to 102°F (37.8°–38.9°C), 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).[11,12]

Pain assessment is more challenging 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-pitched crying, and facial expressions.[13] Such indicators are used in validated assessment scales, such as the FACES scale and FLACC behavioral tools.[14,15] The FACES scale is a visual analog scale, where patients age 3 years and older can select a face that best associates with their current pain level.[14] The FLACC scale, intended for patients of age 2 months to 7 years or those patients unable to communicate pain, is a scale in which a clinician scores a patient based on series of criteria (facial expression, leg movement, activity, crying, and consolability).[15]

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 greater than 10 kg, with a range of 1500 to 2000 mL/m^2 per day. However, a weight-based method of determining normal maintenance fluid requirement for children is often used (Table 2–3).[16]

Patient Encounter Part 1

HM is a 33-week GA premature newborn boy weighing 1.6 kg (3.5 lb), length 39 cm (15.4 in), born to a 25-year-old woman today. HM is currently admitted to the neonatal intensive care unit.

What is HM's weight classification as a neonate?
Calculate HM's corrected age for 6 months from today.
How much maintenance fluid per day (mL) and overall rate (mL/hour), is appropriate at this time for HM?

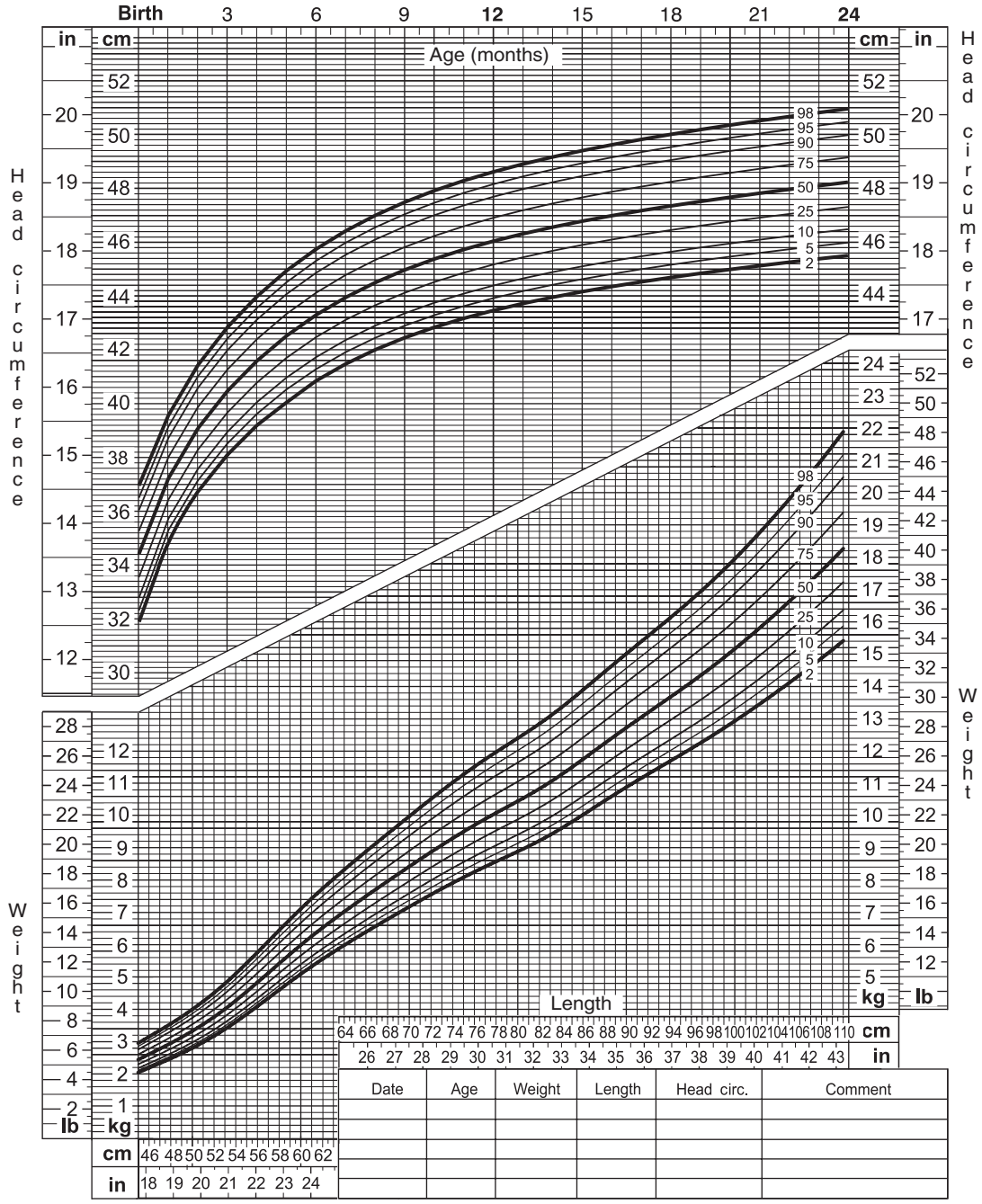

FIGURE 2–1. Example of WHO growth chart of girls, birth to 24 months: Head circumference-for-age and weight-for-length percentile, 2000. (From Centers for Disease Control and Prevention from the WHO Growth Standards. World Health Organization [WHO] Growth Standards are recommended for use in the U.S. for infants and children 0 to 2 years of age. [updated 2010 Sept 9; cited 2020 Nov 16]. Available from: http://www.cdc.gov/growthcharts/who_charts.htm.)

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 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 commonalties between pediatric and adult patients, such as therapeutic serum drug concentrations required to treat certain diseases. For example, target vancomycin serum concentrations needed for treatment of a given infection are often similar between children and adults. Appropriate selection and dosing of drug therapy for a pediatric patient depends on a number of specific factors, such as

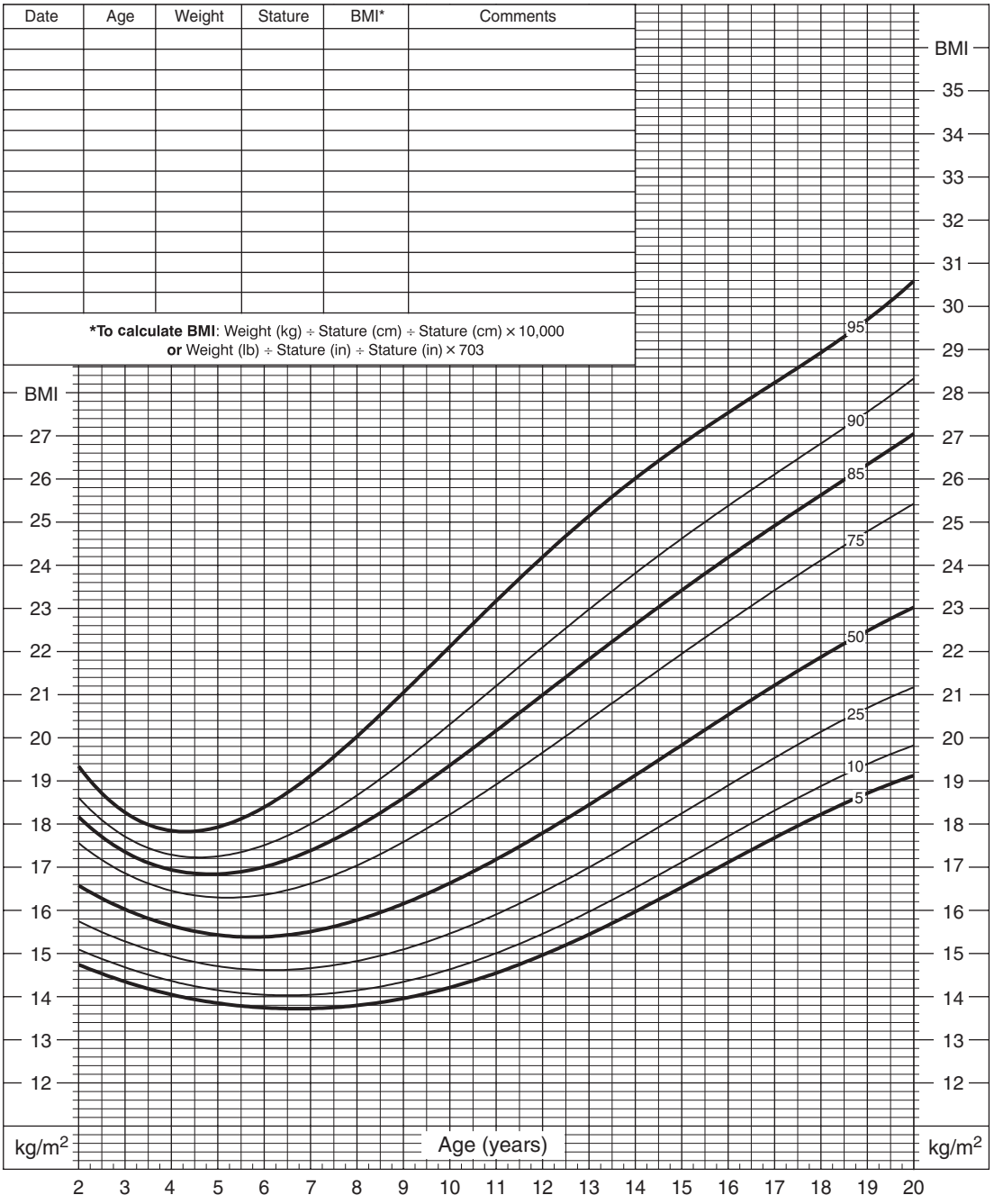

FIGURE 2–2. Example of CDC growth chart of boys, 2 to 20 years: Body mass index for age percentile, 2000. (From Centers for Disease Control and Prevention. CDC Growth Charts. [updated 2016 Dec 7; cited 2020 Nov 16]. Available from: https://www.cdc.gov/growthcharts/cdc_charts.htm.)

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 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 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

Table 2–2

Normal Ranges of Vital Signs (Heart Rate, Respiratory Rate, Blood Pressure) by Age Group[8-10]

Age Group	Heart Rate (Sleep)[a]	Heart Rate (Awake)[a]	Respiratory Rate[b]	Systolic Blood Pressure[c,d]	Diastolic Blood Pressure[c,d]
Neonate (< 28 days)	90–160	100–205	30–60	67–84	31–45
Infant (1–12 months)	90–160	100–190	30–53	72–104	37–56
Toddler (1–2 years)	80–120	98–140	22–37	86–106	42–63
Preschool (3–5 years)	65–100	80–120	20–28	89–112	46–72
School–Age (6–11 years)	58–90	75–118	18–25	97–115	57–76
Adolescent (12–15 years)	50–90	60–100	12–20	102–131	61–83

Note: prematurity can affect values. Values listed are average ranges.

[a]Beats per minute

[b]Breaths per minute

[c]mm Hg

[d]Exact normal values will vary based on age, height, and sex.

may estimate a pediatric dose based on body surface area ratio.

$$\textbf{Approximate pediatric dose} = \textbf{Adult dose} \times [\textbf{BSA (in m}^2\textbf{)} \div \textbf{1.73 m}^2]$$

Limitations for this dose-estimating approach include the need for the patient to be of normal height and weight for age and lack of incorporation of exact pharmacokinetic differences regarding each medication.[17]

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.[18] 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 (GI) mucosa and drug absorption.[18,19] 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 intraluminal hydrolysis.[18] 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 as well as inactive drugs, 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.[18] 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 intravenous (IV) doses of ampicillin and gentamicin for neonatal sepsis.

Intrapulmonary absorption and distribution are 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.[20]

Rectal absorption can also be erratic due to increased peristalsis causing early expulsion of the dosage form in younger patients (ie, infants and young children).[21] 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. High osmolality and large volume of a liquid dosage form may present as a limitation to using an oral liquid formulation for rectal use.

Table 2–3

Maintenance Fluid Calculations by Body Weight[16]

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

Reproduced with permission from Holiday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. Pediatric. 1957;19(5):823–832, by the AAP.

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 decrease with age. Therefore, neonates and infants often require higher individual doses by weight (mg/kg) than older children and adolescents to achieve the same therapeutic serum concentrations.[18] Fluid overload and diuresis can affect V_d and should be assessed for when evaluating drug dosing and pharmacokinetics. The use of extracorporeal membrane oxygenation (ECMO) can further affect 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 clinical and, when available, therapeutic drug monitoring is recommended for those patients requiring ECMO.[22] 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 and ceftriaxone, 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.[23]

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 (CNS) of neonates due to an immature blood–brain barrier.[24]

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 (eg, elixirs) can cause toxicities such as respiratory depression and thus should be avoided, whenever possible, 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.[23] This increase in metabolism slows to adult levels as the child goes through puberty into adulthood.[18]

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. 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.[18] 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. Similarly, due to limited metabolic capacity, propylene glycol, a solvent found in some dosage forms, should be avoided, as toxicity results in serum hyperosmolality, seizures, and respiratory distress.[25] Acetylation via *N*-acetyltransferase reaches adult maturation at around 1 year of life; however, overall activity is dependent on genotypic variability.[18]

Elimination

Nephrogenesis completes at approximately 36 weeks 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.[26]

Creatinine clearance is used as a surrogate marker for GFR; however, there are equations available to estimate GFR in the pediatric population. Pediatric GFR is often calculated to mL/min/1.73 m^2. The Cockroft-Gault, Jelliffe, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, or Modification of Diet in Renal Disease (MDRD) equations for estimating creatinine clearance or GFR in adults should not be used for evaluating patients younger than 18 years. This is due to potential for significant overestimation of GFR and/or lack of validation of these equations in pediatric age ranges, even adolescents. For example, past attempts for proposed application of equations, such as Cockroft-Gault, demonstrated that lack of agreement with measured GFR (via renal scan) in adolescents as young as 13 years of age.[27] The Schwartz's equation was previously used method of estimating pediatric GFR from infancy up to 21 years of age (**Figure 2–3**). This equation uses patient length (cm), serum creatinine (mg/dL) (or μmol/L × 0.0113), and a constant, *k*, which depends on age (including low-birth-weight status for infants).[28] This "original" Schwartz equation is no longer used by many clinicians, due to a change in measurement of serum creatinine methods with calibration traceable to isotope dilution mass spectrometry (IDMS), invalidating the original

"Original Schwartz" Equation

GFR = *k*L/SCr

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

K = proportionality constant
L = length in cm
SCr = serum creatinine in mg/dL
GFR = estimated glomerular filtration rate in mL/min/1.73 m^2

FIGURE 2–3. "Original" Schwartz equation for estimation of glomerular filtration rate (GFR)in pediatric patients up to 21 years of age. (From 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.)

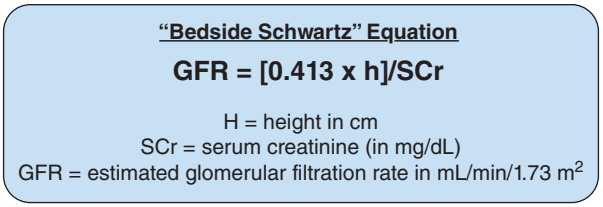

FIGURE 2–4. Bedside Schwartz equation for estimation of glomerular filtration rate (GFR)in pediatric patients ages 1 to 18 years old. (From Staples A, LeBlong R, Watkins CW, Brandt J. Validation of the revised Schwartz estimating equation in a predominantly non-CKD population. Pediatr Nephrol. 2010;25:2321–2326.)

equation's clinical application and can overestimate GFR by up to 40%.[27–31] The preferred method to estimate GFR in children (ages 1–18 years) is the "bedside" Schwartz as it was devised for use with creatinine methods traceable to IDMS (Figure 2–4).[29–31]

Urine output is also a parameter used to assess renal function in pediatric patients. Infants and children with acute kidney injury are likely to present with oliguria or anuria with urine output less than 1 mL/kg/hour.

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; thus, many drugs remain off-label for children.[32] 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] 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. Food and Drug Administration (FDA) regulatory changes provide incentives for a pharmaceutical manufacturer to study and market new drugs for pediatric patients. However, such incentives are not available for generic drugs.

Patient Encounter Part 2

RG is a 1-week-old (weight 3.5 kg [7.7 lb], length 50 cm (19.7 in), no known drug or food allergies), full-term newborn male child admitted to the NICU now presenting lethargy, poor oral intake, and temperature instability. A neonatal sepsis and meningitis rule-out is started. Blood samples, cerebral spinal fluid, and urine were collected for Gram stain and culture, still pending results. Other laboratory results (complete blood count, complete metabolic panel) are still pending. The team requests the consultation regarding empiric antibiotic selection.

The medical resident asks you whether ceftriaxone (highly protein binding) or cefotaxime (low protein binding) should be used as part of the antibiotic regimen to treat RG. Which is the most appropriate and why?

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 not often used due to limited product availability. 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 compounding and stability data are available. Factors such as drug stability, suspendability, dose uniformity, and palatability should be considered when compounding a liquid formulation.[33] Commonly used **suspending agents** include methylcellulose and carboxymethylcellulose (eg, Ora-Plus). Palatability of a liquid formulation can be enhanced by using simple syrup or OraSweet. 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. There may be instances when clinicians may elect to prescribe tablets or capsules that are to be crushed or opened, respectively, and mixed in soft foods. This should be limited to instances when a commercial or compounded liquid dosage form is not appropriate. Additionally, it is important in this scenario, to avoid use of sustained or extended formulations of tablets or capsules. Use should also be limited to wide therapeutic index medications (eg, β-lactam antibiotics) as they have a wide margin of safety, and dose rounding to a certain extent (eg, 10%) is likely feasible to fit an available tablet or capsule strength. To help with palatability of oral medication, some clinicians pair bitter tasting medications (eg, clindamycin) with chocolate flavoring and metallic tasting medications (eg, ferrous sulfate drops) with fruit (eg, citrus) flavoring. 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. Unfortunately, medication errors are common in pediatrics with up to 27% of all pediatric medication orders resulting in an error.[34] 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.[35] 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. Electronic health records (EMR) with clinical decision support systems and barcoding 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.[34]

Prevention of medication errors is a joint effort between healthcare 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/Alternative and Over-the-Counter Medication Use

Between 30% and 70% of children with a chronic illness (eg, asthma, attention deficit hyperactivity disorder, autism, cancer) or disability use CAMs. 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 healthcare providers.[36] 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 colic; however, parents may be advised by family and friends to use products that may have harmful additive ingredients. Gripe water is an oral solution containing a combination of ingredients, such as chamomile and sodium bicarbonate, and is not regulated by the FDA. 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.[37,38] 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.[39,40] 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. Signs or symptoms of Reye syndrome, usually appearing several days after start of a viral infection, are relatively nonspecific, including diarrhea, persistent vomiting, increased respiratory rate, increasing lethargy, and seizure. 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's 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 liquid amount or available tablet/capsule strength 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. Studies have demonstrated less error in dose measurement using an oral syringe compared to other devices (eg, dosing cup, dropper, dosing spoon) and that in addition to appropriate device caregiver health literacy contributes to potential for medication dose measurement error.[41] Due to inconsistencies and risk for possible inaccuracy of measuring smaller doses, dosing or measuring spoons, oral droppers, and medicine cups are not recommended for measuring doses for infants and young children. Household dining or measuring spoons are not accurate or consistent and should not be used for the administration of oral liquids. Additionally, consistency in dosing units used for liquid formulation (eg, milliliters instead of teaspoons or ounces) is necessary to minimize further medication dosing errors.[42] Individuals in supervision of infants and children attending daycare and schools should also be educated about medication administration. Guidelines with regard to medication use in school settings are available.[43–45]

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 2–4.[46]

Table 2–4

Helpful Tips for Medication Administration for Selected Dosage Forms[46]

Dosage Form	Recommendations
Ophthalmic drops or ointment	• Wash hands thoroughly prior to administration • Position child laying down in supine position • Avoid contact of applicator tip to surfaces, including the eye • Drops should be placed in the pocket of the lower eyelid • Ointment strip should be placed along the pocket of the lower eyelid

Otic drops	• Wash hands thoroughly prior to administration
	• Position child laying down in prone position
	• Tilt head to expose treated ear, gently pull outer ear outward, then due to age-dependent change in angle of eustachian tube:
	  • If child < 3 years of age, gently pull downward and back; apply drops
	  • If child is > 3 years of age, gently pull upward and back; apply drops

Nasal drops	• Wash hands thoroughly prior to administration • Position child laying down in supine position • Slightly tilt head back; place drops in nostril(s) • Remain in position for appropriate distribution of medication
Rectal suppository	• Similar to adult administration; challenging route for administration • For younger patients (ie, < 3 years), a smaller finger (eg, pinky finger) should be used to insert suppository
Metered-dose inhalers	• Use a spacer • For younger children, use one with a mask, be sure the mask is secured/placed closely up against the child's face, avoiding gaps between face and mask and creating a seal to ensure medication delivery • Child should take slow breaths in with each dose • Wait at least 1 minute between doses

From Buck MI, Hendrick AE. Pediatric Medication Education Text, 5th ed. American College of Clinical Pharmacy, 2009; Sec1: xvii–xxvii.

Patient Encounter Part 3

DD is a 13-year-old adolescent boy who is brought to the clinic with a weeklong history of productive cough, rhinorrhea, and congestion. The child's temperature last night was 39°C (102.2°F) by electronic axial thermometer. Mom reports to have given the child several doses of acetaminophen, but symptoms did not improve and thus she brought him to be seen. Patient has history of allergic rhinitis and eczema. The pediatrician diagnoses DD with community-acquired pneumonia requiring antibiotic treatment and asks you to develop a treatment care plan for DD including use of cefdinir 14 mg/kg/dose by mouth divided twice a day for 10 days.

What additional information would you need to develop an appropriate treatment care plan for DD?

Mom asks you if acetaminophen was the right choice for DD's fever and pain and if other options such as aspirin could be used instead. What would you recommend for pain and fever for DD? Why?

The medical assistant provides you DD's weight as 85.8 lb (39 kg). Mom states that DD would prefer a liquid form as he is still working on swallowing pills. Cefdinir is available as a 125 mg/5 mL or 250 mg /5 mL suspension. What is the most appropriate dosage strength and calculated dose of cefdinir for DD?

Two days later, Mom calls the clinic stating that DD did not like the taste of cefdinir and would like to change to a capsule or tablet. Cefdinir comes as a 300-mg capsule. Explain whether or not this change is appropriate.

Accidental Ingestion in Pediatric Patients

Pediatric accidental ingestions most often occur in the home. 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 harmful substances are stored (eg, medication cabinets). Indeed, caregivers are encouraged to use "child-safe" devices to lock closets and cabinets to reduce risk of accidental ingestions; however, this is not a substitute for appropriate caregiver supervision.

Ingested substances can vary, from household cleaning solutions to prescription and nonprescription medications. The most common exposures in children younger than 5 years were cosmetics/personal care products, analgesics, household cleaning substances, foreign bodies (eg, small toys), and topical preparations.[47] Unintentional or accidental ingestions are the most common type in younger children (ie, younger than 5 years) with fatalities possible with as little as one to two tablets/capsules of medications such as calcium channel blockers, tricyclic

Patient Care Process

Collect Information:

- For patients up to 2 years of age, review birth history, including gestational age, birth weight, medical complications, postnatal age, and corrected age.
- Review patient's past medical history, comorbidities.
- Review patient's available laboratory data (eg, serum creatinine, liver function tests).
- Review all current medication therapy, including CAM and OTC.
- Review patient's medication allergies and/or intolerances.

Assess the Information:

- Assess appropriateness of therapy. Is patient on appropriate drug therapy for current diagnoses? Are current medication doses appropriate (ie, for age, weight, etc.)? Any medications without indication?
- Evaluate patient's organ function (renal and hepatic), including use of appropriate equations (eg, bedside Schwartz).
- Assess current therapy for safety and efficacy. Is the medication effective for this patient? Is the patient experiencing any adverse effects?
- Consider available data regarding safe and effective dosing of selected drug.
- Assess patient's (or patient's caregiver) history of medication adherence and health care beliefs.

Develop a Care Plan:

- Consider available routes of administration. What is the most appropriate route? If IV medication is needed, what types of IV accesses are available? For example, does the patient have a central or peripheral line? Determine if IV medication needs to be further diluted or concentrated based on patient's comorbidities and fluid status.
- Consider ease of administration for the patient and/or caregiver. Is the dose easily measurable? Is the dosing frequency reasonable for their family schedule?
- Verify accuracy of dose calculations. Verify current weight and dosing units (e.g., mg/kg/day, mg/kg/dose). Is the dosing interval appropriate?
- Determine what drug-drug/drug-food interactions are possible with this new therapy. How can they be managed?

Implement the Care Plan:

- Communicate plan for care with patient care team.
- Educate parent/caregiver/patient regarding selected drug therapy including purpose, dose, administration, duration therapy, possible side effects, etc.

Follow-up: Monitor and Evaluate:

- Monitor signs and symptoms of clinical outcomes (improvement and decline). Measure drug serum concentrations when appropriate. Monitor for possible adverse drug events.
- Reinforce patient/caregiver education.

antidepressants, or opioids. For those age between 13 and 19 years and older, intentional exposures outnumber those classified as unintentional/accidental and include recreational and self-harm attempts.[47] Management of accidental ingestions varies depending on the ingested substance, the amount, and the age and size of the child. The American Academy of Clinical Toxicology and the AAP do not recommend the use of ipecac syrup for treatment of accidental ingestion; thus, inducing emesis is not a recommended approach for any type of ingestion.[48] Clinicians receiving calls regarding management of accidental ingestions, depending on severity of case, should direct them to the emergency department for evaluation and/or the local or regional poison control center for specific recommendations, which can reached via a universal contact number (1-800-222-1222), with additional information located through the American Association of Poison Control Centers (*www.aapcc.org*).[49]

Abbreviations Introduced in This Chapter

AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
bpm	Beats per minute
CAM	Complementary and alternative medicine
CDC	Centers for Disease Control and Prevention
CPOE	Computer physician order entry
ELBW	Extremely low birth weight
GA	Gestational age
GFR	Glomerular filtration rate
LBW	Low birth weight
MDI	Metered-dose inhaler
OTC	Over-the-counter
V_d	Volume of distribution (apparent)
VLBW	Very low birth weight

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