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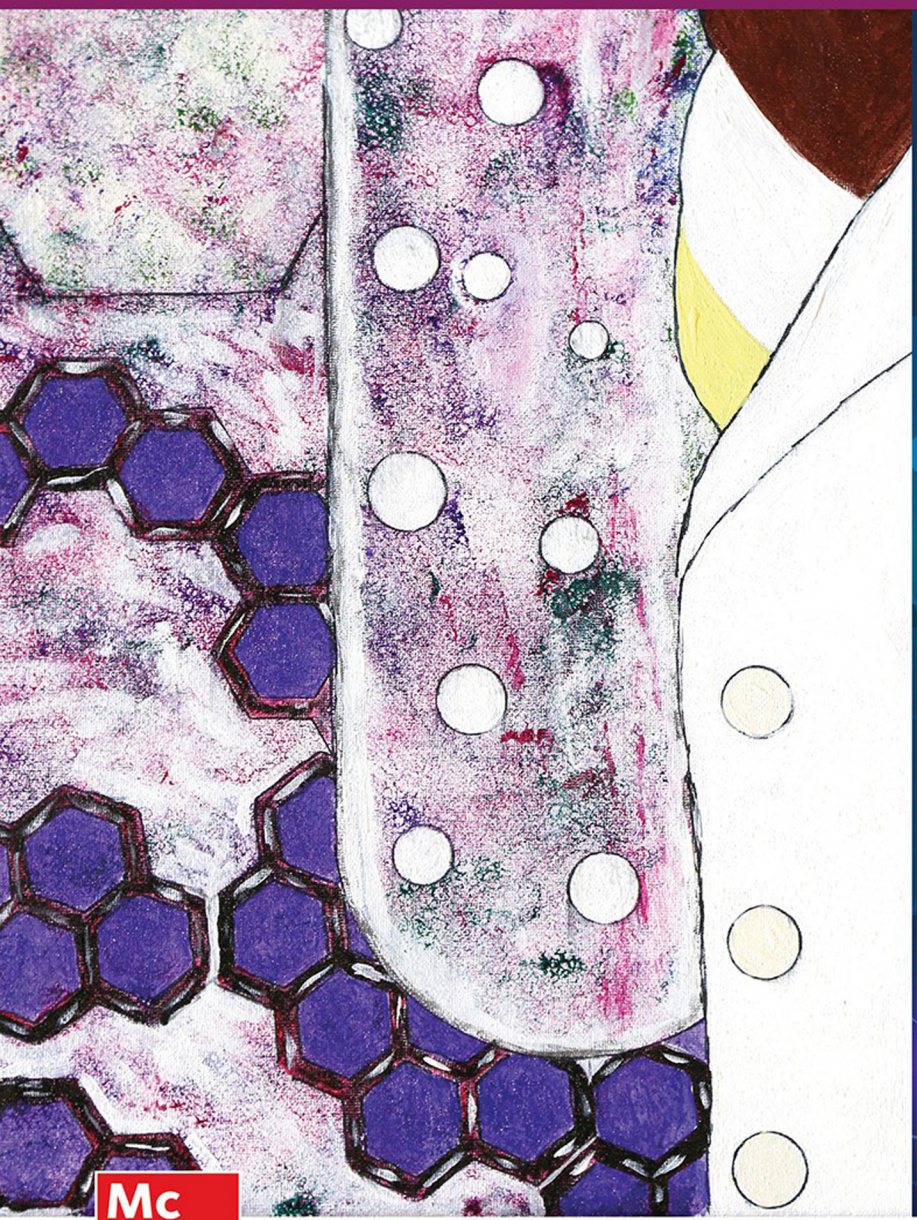

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Pharmacotherapy Principles & Practice

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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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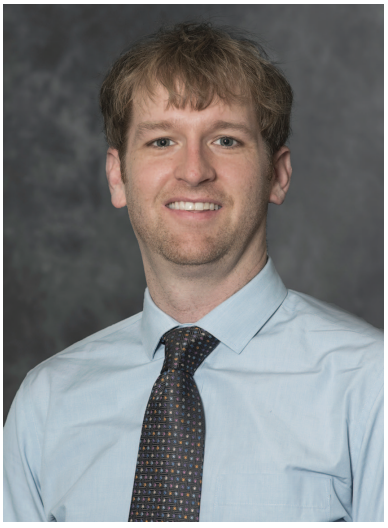

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PREFACE

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?

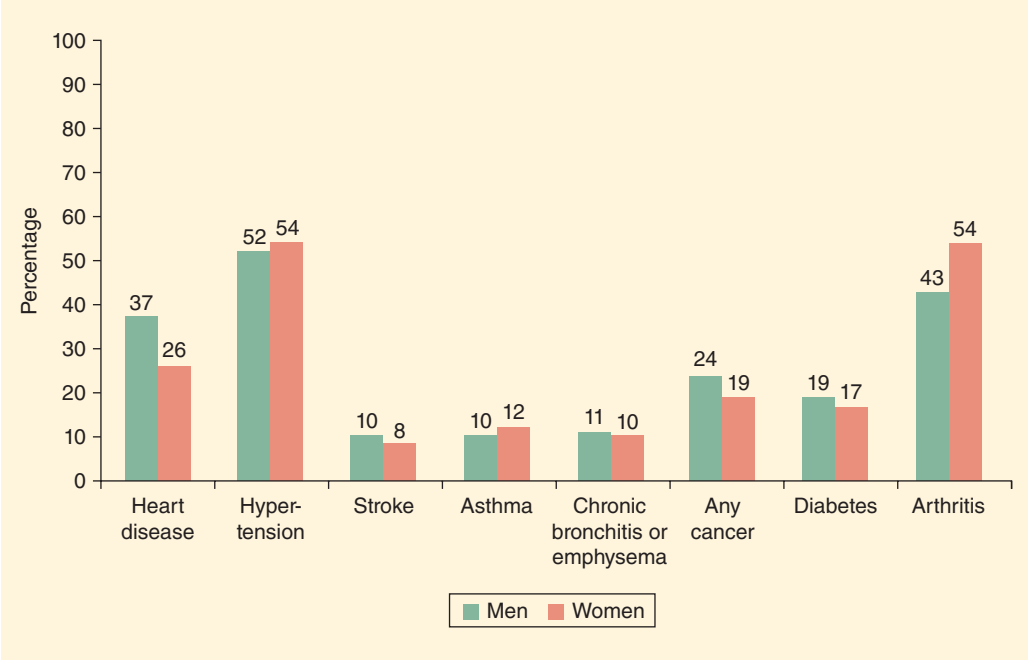

FIGURE 1–1. Percentage of people 65 years and older who reported having selected chronic conditions, by sex, 2005 to 2006. Note: Data are based on a 2-year average from 2005 to 2006. Reference population: These data refer to the noninstitutionalized population. (From Centers for Disease Control and Prevention,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