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LEHNE'S PHARMACOTHERAPEUTICS

for Advanced Practice Nurses and Physician Assistants

THIRD EDITION

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LEHNE'S PHARMACOTHERAPEUTICS

for Advanced Practice Nurses and Physician Assistants

THIRD EDITION

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In remembrance of Victoria "Vicki" Erickson,
a nursing leader, mentor, colleague, and friend.
You are missed by many.
LDR

To my remarkable students.
It excites me to know that the future of nursing is in your most capable hands.
JRB

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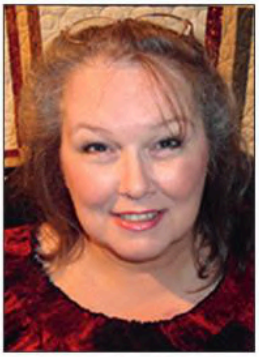

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PREFACE

Pharmacology and pharmacotherapeutics pervade all phases of advanced practice nursing and physician assistant practice and relate directly to patient care and education. Despite their importance, many students—and even some teachers—are often uncomfortable with these subjects because traditional textbooks have stressed *memorizing* rather than *understanding*. In this book, the guiding principle is to establish further understanding of drugs and their use in patient care.

This textbook has two major objectives: to help you establish a continued knowledge base in the basic science of drugs and to show you how that knowledge can be applied in clinical practice. The methods by which these goals are achieved are described here.

LAYING FOUNDATIONS IN BASIC PRINCIPLES

To understand drugs, you need a solid foundation in basic pharmacologic principles. To help you establish that foundation, the book has major chapters on the following topics: basic principles that apply to all drugs (Chapters 4 through 7), basic principles of drug therapy across the life span (Chapters 8 through 10), basic principles of neuropharmacology (Chapter 11), and basic principles of antimicrobial therapy (Chapter 72).

REVIEWING PHYSIOLOGY AND PATHOPHYSIOLOGY

To understand the actions of a drug, it is useful to understand the biological systems that the drug influences. Accordingly, for all major drug families, relevant physiology and pathophysiology are reviewed. In almost all cases, these reviews are presented at the beginning of each chapter rather than in the systems review at the beginning of a unit. This juxtaposition of pharmacology, physiology, and pathophysiology is designed to help you understand how these topics interrelate.

TEACHING THROUGH PROTOTYPES

Within each drug family, we can usually identify a prototype—that is, a drug that embodies characteristics shared by all members of the group. Because other family members are similar to the prototype, to know the prototype is to know the basic properties of all family members.

The benefits of teaching through prototypes can be appreciated with an example. Let's consider the nonsteroidal antiinflammatory drugs (NSAIDs), a family that includes aspirin, ibuprofen (Motrin), naproxen (Aleve), celecoxib (Celebrex), and more than 20 other drugs. Traditionally, information on these drugs is presented in a series of paragraphs describing each drug in turn. When attempting to study from such a list, you are likely to learn many drug names and little else; the important concept of similarity among family members is easily lost. In this book, the family prototype—aspirin—is discussed first and in depth. After this, the small ways in which individual NSAIDs differ from aspirin are pointed out. This approach is not only more efficient than the traditional approach but also more effective, in that similarities among family members are emphasized.

USING CLINICAL REALITY TO PRIORITIZE CONTENT

This book contains two broad categories of information: pharmacology (i.e., basic science about drugs) and therapeutics (i.e., clinical use of drugs). To ensure that content is clinically relevant, we use evidence-based treatment guidelines as a basis for deciding what to stress and what to play down. Unfortunately, clinical practice is a moving target: When effective new drugs are introduced and clinical trials reveal new benefits or new risks of older drugs, the guidelines change—and so we must work hard to keep this book current. Despite our best efforts, the book and clinical reality may not always agree. We therefore encourage you to use this book as a textbook in order to understand how particular drug classes are used therapeutically, but to rely on continually updated drug resources for day-to-day prescribing.

SPECIAL FEATURES

Summary of Key Prescribing Considerations: These summaries provide guidance for safe prescribing practices and include information such as baseline data collection, monitoring needs, identification of high-risk patients, and evaluation for therapeutic effects.

Prototype Drugs: Denoted in teal boxes; these key drugs are easy to locate.

Black Box Warnings: This feature draws the reader's attention to important safety concerns related to contraindications and adverse effects.

Patient Education: These boxes offer important information to provide to patients regarding their therapy.

Person-Centered Care Across the Life Span: These boxes in many chapters highlight care concerns for patients throughout their lives, from infancy to older adulthood.

Canadian trade names are identified by a **maple leaf icon.**

TEACHING SUPPLEMENTS FOR INSTRUCTORS

The Instructor Resources are available online and include a **Test Bank**, a **PowerPoint Collection**, and an **Image Collection.**

STUDENT RESOURCES

Student Resources: New online student resources include one **Case Study** and **Review Questions** per textbook section.

WAYS TO USE THIS TEXTBOOK

Thanks to its focus on essentials, this book is especially well suited to serve as the primary text for a course dedicated specifically to pharmacology and pharmacotherapeutics. In addition, the book's focused approach makes it a valuable resource for pharmacologic instruction within an integrated curriculum and for self-directed learning by students, teachers, and practitioners.

How is this focus achieved? Four primary techniques are employed: (1) teaching through prototypes, (2) limiting discussion of adverse effects and drug interactions to information that matters most, and (3) using evidence-based clinical guidelines to determine what content to stress.

Students often feel that pharmacology is one of the most difficult classes to master. Pharmacotherapeutics can be an unpopular subject because of the vast and rapidly changing area of content. We hope that this book makes the subjects of pharmacology and pharmacotherapeutics easier for you to master and more enjoyable for you to understand by allowing you to focus on the most important umbrella concepts of pharmacology and pharmacotherapeutics as they relate to the care and safety of patients and the management of their health problems.

Laura D. Rosenthal
Jacqueline Rosenjack Burchum

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UNIT XIII Drugs for Bone and Joint Disorders

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1

Prescriptive Authority

Our purpose in writing this book is to prepare advanced practice providers to provide safe and competent medication therapy to patients. This role requires the ability to select, prescribe, and manage medications. In this chapter we examine issues surrounding prescriptive authority and how those issues affect this fundamental aspect of comprehensive patient care.

WHAT IS PRESCRIPTIVE AUTHORITY?

Prescriptive authority is the legal right to prescribe drugs. Full prescriptive authority affords the legal right to prescribe independently and without limitation. Physicians have full prescriptive authority. For nonphysician providers, the degree of prescriptive authority varies. Some have full prescriptive authority; however, for many, prescriptive authority is restricted. Limitations are generally tied to oversight by a doctor of medicine (MD) or doctor of osteopathy (DO) as part of the provider's scope of practice.

Recall that there are two components of prescriptive authority: (1) the right to prescribe independently and (2) the right to prescribe without limitation. The provider who prescribes independently is not subject to rules requiring physician supervision or collaboration. The provider who prescribes without limitation may prescribe any drugs, including controlled drugs, with the exception of schedule I drugs, which have no current medical use.

Full practice authority is sometimes interpreted differently for advanced practice registered nurses (APRNs) and physician assistants[a] (PAs) because supervisory requirements vary for the two professions. PAs are required to have an affiliation with a physician in order to practice and prescribe. All PAs, including those in a solo practice, must establish a relationship with physician who serves in a supervisory or collaborative role and who can be reached by telephone or other means of telecommunication. (See *PA State Laws and Regulations* available at https://www.aapa.org/advocacy-central/state-advocacy/state-laws-and-regulations for additional information.) If the PA–physician arrangement does not limit drugs that may be prescribed and if the law allows the PA to prescribe schedule II to V drugs, the PA may enjoy a type of quasifull prescriptive authority. Indeed, some have referred to this as full prescriptive authority; however, the issue of being affiliated with a physician still applies. Hence PAs do not have the legal right to prescribe without the PA–physician arrangement. Even for those in solo practice, there is always the possibility of dissolution of the PA–physician arrangement. In the event this occurs, the PA must affiliate with another physician or physician group to continue prescribing.

Whether APRNs possess full prescriptive authority depends on their legal right to prescribe without a supervisory or collaborative requirement. APRNs are *educated* to practice and prescribe independently without supervision; however, some state laws require that they practice in collaboration with or under the supervision of a physician. In these situations, some physicians limit the types of drugs that the APRN can prescribe. State laws may place additional restrictions with regard to controlled drugs.

Table 1.1 provides prescriptive authority status for certified midwifes and nurse practitioners. Table 1.2 provides prescriptive authority status for PAs. Table 1.3 provides this information for certified registered nurse anesthetists. Information regarding the right to prescribe controlled drugs is available at http://www.deadiversion.usdoj.gov/drugreg/practioners.

PRESCRIPTIVE AUTHORITY REGULATIONS

Prescriptive authority is determined by state law. As a result of differences from state to state, advanced practice providers may have full prescriptive authority in some states yet face significant restrictions in other states. The stark differences particularly affect providers who serve in *locum tenens* (temporary) staffing positions or who have practices in two contiguous states.

The regulation of prescriptive authority is under the jurisdiction of a health professional board. This may be the State Board of Nursing, the State Board of Medicine, or the State Board of Pharmacy, as determined by each state.

Although the federal government controls drug regulation, it has no control over prescriptive authority. However, several organizations have appealed for changes that would place scope of practice and prescriptive authority under federal regulation in an effort to expand prescriptive authority and the scope of practice of advanced practice providers. For example, National Academy of Medicine (formerly the Institute of Medicine or IOM) advocated for federal regulation in their report, *The Future of Nursing: Leading Change, Advancing Health.* After noting problems with the "patchwork of state regulations," they wrote:

> *Some states have kept pace with the evolution of the health care system by changing their scope-of-practice regulations to allow nurse practitioners to see patients and prescribe medications without a physician's supervision or collaboration. However, the majority of state laws lag behind in this regard. … The federal government*

[a]In May, 2021, the AAPA (American Association of Physician Associates, formerly American Association of Physician Assistants) passed a resolution adopting the name physician associate as the official title for PAs. The reason we use physician assistant in this book is based on AAPA advice which states, "PAs should continue to use 'physician assistant' or 'PA' as their official legal title in a professional capacity … until the jurisdiction governing their licensure and practice has formally adopted the title of 'physician associate.'" (See https://www.aapa.org/title-change/general-faqs.)

TABLE 1.1 Advanced Practice Registered Nurse: Nurse Midwife and Nurse Practitioner Practice and Prescriptive Authority by State

State	Scheduled Drugs	Physician Relationship Required	Transition to Independent Practice and Prescribing Period Required	Full Independent Practice Authority but Physician Relationship Required for Prescriptive Authority	Full Independent Practice Authority but Transition to Independent Prescribing Period	Full Independent Practice and Prescriptive Authority
AL	III–V, limited II	CNM, NP				
AK	II–V					CNM, NP
AZ	II–V					CNM, NP
AR	III–V, limited II		NP			CNM
CA	II–V		NP	CNM		
CO	II–V				CNM, NP	
CT	II–V		NP			CNM
DE	II–V					CNM, NP
FL	II–V		CNM, NP			
GA	III–V	CNM, NP				
HI	II–V					CNM, NP
ID	II–V					CNM, NP
IL	II–V		CNM, NP			
IN	II–V (within limits)	CNM, NP				
IA	II–V					CNM, NP
KS	II–V					CNM, NP
KY	II–V			CNM, NP		
LA	III–V, limited II	CNM, NP				
ME	II–V		NP			CNM
MD	II–V		NP			CNM
MA	II–V				NP	CNM
MI	II–V	NP		CNM		
MN	II–V		NP			CNM
MS	II–V	CNM, NP				
MO	III–V, limited II	CNM, NP				
MT	II–V					CNM, NP
NE	II–V	CNM	NP			
NV	II–V					CNM, NP
NH	II–V					CNM, NP
NJ	II–V	CNM		NP		
NM	II–V					CNM, NP
NY	II–V		NP			CNM
NC	II–V	CNM, NP				
ND	II–V					CNM, NP
OH	II–V	CNM, NP				
OK	III–V			CNM, NP		
OR	II–V					CNM, NP
PA	II–V	CNM, NP				
RI	II–V					CNM, NP
SC	II–V	CNM, NP				
SD	II–V					CNM, NP
TN	II–V	CNM, NP				
TX	III–V, limited II	CNM, NP				
UT	II-V			CNM		NP
VT	II–V		CNM, NP			
VA	II–V		CNM, NP			
WA	II–V					CNM, NP
WV	II–V				CNM, NP	

TABLE 1.1 Advanced Practice Registered Nurse: Nurse Midwife and Nurse Practitioner Practice and Prescriptive Authority by State—cont'd

State	Scheduled Drugs	Physician Relationship Required	Transition to Independent Practice and Prescribing Period Required	Full Independent Practice Authority but Physician Relationship Required for Prescriptive Authority	Full Independent Practice Authority but Transition to Independent Prescribing Period	Full Independent Practice and Prescriptive Authority
WI	II–V	CNM, NP				
WY	II–V					CNM, NP

CNM, Certified nurse midwife; *NP*, certified nurse practitioner.
Adapted from U.S. Health Resources and Services Administration (HRSA). (2023). *NCSL Scope of Practice Policy Advanced Practice Registered Nurses: Nurse Practitioner Practice Authority*. https://scopeofpracticepolicy.org/practitioners/advanced-practice-registered-nurses/sop/nurse-practitioner-practice-authority; HRSA. *NCSL Scope of Practice Policy Advanced Practice Registered Nurses: Certified Nurse Midwife Practice Authority.* (2023). https://scopeofpracticepolicy.org/practitioners/advanced-practice-registered-nurses/sop/certified-nurse-midwife-practice-authority; and Drug Enforcement Agency. *Mid-Level Practitioners—Controlled Substance Authority by Discipline Within State.* (2023). https://www.deadiversion.usdoj.gov/drugreg/practioners/mlp_by_state.pdf.

TABLE 1.2 Physician Assistant Practice and Prescriptive Authority by State[a]

State	Scheduled Drugs	Physician Supervision Required for Practice and Prescriptive Authority	Physician Collaboration Allowed for Practice and Prescriptive Authority	Supervision or Collaboration Not Required for Practice or Prescriptive Authority
AL	II–V	✓		
AK	II–V		✓	
AZ	II–V		✓	
AR	II-V	✓		
CA	II–V	✓		
CO	II–V		✓	
CT	II–V	✓		
DE	II–V		✓	
FL	II–V	✓		
GA	III–V	✓		
HI	III–V	✓		
ID	II–V		✓	
IL	II–V		✓	
IN	II–V		✓	
IA	II–V			✓
KS	II–V	✓		
KY	None	✓		
LA	II–V	✓		
ME	II–V		✓	
MD	II–V		✓	
MA	II–V	✓		
MI	II–V		✓	
MN	II–V		✓	
MS	II–V	✓		
MO	III–V	✓		
MT	III–V			✓
NE	II–V	✓		
NV	II-V	✓		
NH	II–V		✓	
NJ	II–V	✓		
NM	II–V		✓	
NY	II–V	✓		
NC	II-V	✓		
ND	II-V			✓
OH	II–V	✓		
OK	II–V	✓		
OR	II–V		✓	

Continued

TABLE 1.2 Physician Assistant Practice and Prescriptive Authority by State—cont'd

State	Scheduled Drugs	Physician Supervision Required for Practice and Prescriptive Authority	Physician Collaboration Allowed for Practice and Prescriptive Authority	Supervision or Collaboration Not Required for Practice or Prescriptive Authority
PA	II–V	✓		
RI	II–V		✓	
SC	II–V	✓		
SD	II–V	✓		
TN	II–V		✓	
TX	III–V	✓		
UT	II–V			✓
VT	II–V		✓	
VA	II–V		✓	
WA	II–V	✓		
WV	III–V		✓	
WI	II–V		✓	
WY	II–V			✓

[a]Physician assistants (PAs) are required to have a PA–physician relationship that is detailed in a written practice agreement.
Adapted from Health Resources and Services Administration. (2023). *NCSL Scope of Practice Policy.* https://scopeofpracticepolicy.org/practitioners/physician-assistants; and Drug Enforcement Agency. (2023). *Mid-Level Practitioners—Controlled Substance Authority by Discipline Within State.* https://www.deadiversion.usdoj.gov/drugreg/practioners/mlp_by_state.pdf.

TABLE 1.3 Certified Registered Nurse Anesthetist Prescriptive Authority by State

State	Physician Relationship Required or Prescriptive Authority Limited	Independent Prescriptive Authority	No Prescriptive Authority
AL			✓
AK		✓	
AZ	✓		
AR	✓		
CA			✓
CO	✓		
CT	✓		
DE		✓	
FL	✓		
GA			✓
HI		✓	
ID		✓	
IL	✓		
IN			✓
IA		✓	
KS			✓
KY	✓		
LA	✓		
ME	✓		
MD		✓	
MA	✓		
MI	✓		
MN		✓	
MS			✓
MO	✓		
MT		✓	
NE			✓
NV			✓
NH		✓	
NJ	✓		
NM		✓	
NY			✓
NC			✓

TABLE 1.3 Certified Registered Nurse Anesthetist Prescriptive Authority by State—cont'd

State	Physician Relationship Required or Prescriptive Authority Limited	Independent Prescriptive Authority	No Prescriptive Authority
ND		✓	
OH	✓		
OK	✓		
OR		✓	
PA			✓
RI			✓
SC			✓
SD		✓	
TN	✓		
TX	✓		
UT			✓
VT		✓	
VA	✓		
WA		✓	
WV	✓		
WI	✓		
WY		✓	

Adapted from American Association of Nurse Anesthesiology (AANA) State Government Affairs Division. (2023). *Prescriptive Authority Map.* https://www.aana.com/wp-content/uploads/2023/04/CRNA-Prescriptive-Authority-1.png.

has a compelling interest in the regulatory environment for health care professions because of its responsibility to patients covered by federal programs. … Equally important is the responsibility to all American taxpayers who fund the care provided under these programs to ensure that their tax dollars are spent efficiently. … Scope-of-practice regulations in all states should reflect the full extent not only of nurses but of each profession's education and training. (https://nap.nationalacademies.org/download/12956)

THE CASE FOR FULL PRESCRIPTIVE AUTHORITY

- Advanced practice providers complete rigorous programs of study, largely in accredited programs that meet stringent national standards. Although there are differences in each program, all include common components. For example, they require extensive education focused on assessment, diagnosis, and management of health problems. Diagnostic reasoning, critical thinking, and procedural skills are evaluated in both didactic and clinical courses. National examinations validate the ability to provide safe and competent care. Licensure ensures that providers comply with standards of practice that promote public health and safety. In short, advanced practice providers are prepared to fully implement the advanced practice role in their profession.
- Limited prescriptive authority creates numerous barriers to quality, affordable, and accessible patient care. For example, restrictions on the distance of the APRN or PA from the physician providing supervision or collaboration may prevent outreach to areas of greatest need. A requirement to obtain the physician's cosignature on prescriptions can increase patient waits. Despite the use of terms such as *collaborative* arrangement, these relationships create a situation in which one partner holds the power. In the event of dissolution of the arrangement, the ultimate loss is commonly assumed by the advanced practice provider rather than the physician.
- In 2021, the Association of American Medical Colleges released a report projecting the future of the physician workforce, *The Complexities of Physician Supply and Demand: Projections from 2019 to 2034* (https://www.aamc.org/media/54681/download). Several key findings have important implications for nonphysician providers.
- By 2034, the shortage of physicians is projected to range between 37,800 and 124,000. In primary care alone, a 17,800 to 48,000 physician shortage is anticipated. *(The lower numbers on these ranges reflect an increase in APRNs and PAs used to help offset physician shortages.)*
- The report notes, "The supply of advanced practice registered nurses (APRNs) and physician assistants (PAs) continues to grow rapidly, along with improved understanding of their value in care delivery and in helping improve access to care for underserved populations" and "A growing body of literature, both in the United States and internationally, indicates APRNs and PAs provide high-quality care, increase physician productivity, and, in some specialties, perform many of the same functions as physicians …"
- In the wake of this realization, implementation of the Affordable Care Act has increased the demand for provider coverage. The recent and ongoing COVID-19 (coronavirus disease identified in 2019) crisis has also highlighted the necessity of preparing for an uncertain future.
- In these scenarios, in which physician demands are excessive, requiring oversight for other providers may be untenable. To adequately meet the demands for future health care needs, APRNs and PAs will need broader practice privileges than some states currently allow. This includes an imperative to allow full prescriptive authority.

PRESCRIPTIVE AUTHORITY AND RESPONSIBILITY

The possession of full prescriptive authority requires a somber responsibility. Whether you are reading this book as a student or as a practicing provider, it is essential to recognize the full obligation this requires. The safe and competent practice of prescribing and managing medications requires a sound understanding of drugs and the conditions that they are used to manage. It is our goal to help you lay that foundation. In the coming chapters, you will read about rational drug selection, writing prescriptions, and promoting positive outcomes. Then we will delve into the heart of pharmacology through a study of pharmacokinetics and pharmacodynamics as we prepare you for the study of individual drug categories.

2

Rational Drug Selection and Prescription Writing

RESPONSIBILITY OF PRESCRIBING

As a practitioner, you will assume great responsibility when caring for patients. The ability to prescribe medications is both a privilege and a burden. Although you may be familiar with many drugs through your previous practice as a registered nurse or other member of the health care field, giving medications and prescribing medications are two very different things. There are many different issues to consider when writing a prescription, many of which we discuss in this chapter or in the previous chapter regarding prescriptive authority.

The best way to keep your patients (and yourself) safe is to be prudent and deliberate in your decision-making process. Have a documented provider–patient relationship with the person for whom you are prescribing. Do not prescribe medications for family or friends or for yourself. Document a thorough history and physical examination in your records. Include any discussions you have with the patient regarding risk factors, side effects, or therapy options. Have a documented plan regarding drug monitoring or titration, if applicable. If you consult additional providers, note that you did so. Finally, use the references provided in Box 2.1 to assist in safely and rationally choosing one medication over another.

DRUG SELECTION

Cost

The cost of medications in the United States has risen steeply within the past 10 years. Increasing cost is related to multiple factors, including corporate competition. It is also noted that one of the reasons people do not adhere to their prescribed medication regimen is its excessive cost. Often, we are so concerned with obtaining the right diagnosis and making our patient well that we overlook key pieces of information, including patient financial status. When patients cannot afford the drug you prescribe, they may not get well, even though they want to be compliant. It is of critical importance that providers ask patients if they have difficulty obtaining their medication because it is cost prohibitive.

If you find that your patient is having difficulty purchasing the prescribed medications, consider changing pharmacies or drug regimens. The cost of a drug can vary widely between pharmacies, even within the same city. Many corporations have created generic $4 lists or special prescription programs that allow patients to fill their medications for a reasonable cost. In addition, all health plans through the Affordable Care Act (ACA) are required to include prescription drug coverage, although these vary greatly. As a prescriber, you need to be familiar with the local resources for medication assistance and low-cost medications.

Guidelines

When in doubt, follow current guidelines for the treatment of a particular disease or symptom. Almost all medical and nursing societies have published guidelines, including the American Heart Association, the American College of Cardiology, the Infectious Diseases Society of America, and the American Diabetes Association. It is the provider's responsibility to keep abreast of new recommendations or changes in guidelines and to incorporate these into their prescribing practices. Although closely following the guidelines is desirable, we must always take into account that our patients may not fit well into these guidelines and that individualized care is always best. In these cases, it is important to document the rationale for deviating from standard of care.

Availability

Every facility and pharmacy provides drugs according to a formulary. This formulary is selected by a panel of pharmacists and providers and may be subject to following guidelines created by regulatory agencies, such as the Centers for Medicare and Medicaid Services (CMS). The formulary may also depend on regional and national drug supplies, drug costs and available rebates, and the presence of generic medications on the market.

In short, the drug you want may not be available in your facility or at a specific pharmacy. This can affect your choice in medications. Become familiar with the formulary where you are employed and know that it can change over time. Often there are substitutes or similar medications you can order in place of what you originally intended. For example, omeprazole may be indicated for the treatment of erosive esophagitis, but the formulary contains esomeprazole instead.

Interactions

As noted throughout this text, there are few medications that do not interact with either another medication or a food. Polypharmacy greatly increases the risk for interactions. Some of these interactions are negligible, but some can have life-threatening consequences. It is of crucial importance to ask the patient about *all* current drugs, including over-the-counter (OTC) medications and herbal preparations. Many patients do not consider OTC or alternative pharmaceuticals as "medications" and may not mention them unless you ask specifically.

When adding a new medication to a patient regimen, check for significant interactions. There are many resources that allow checks for interactions between multiple medications or foods at one time. If there is a low-risk interaction identified, you may find it acceptable to discuss this with your patient, document the conversation, and then prescribe the medication. If there is a relative or absolute contraindication to the proposed drug combination, it is best to choose an alternative if at all possible.

Side Effects

All drugs have side effects. Some are adverse, and some may be beneficial. In addition, one patient may experience adverse effects to a

BOX 2.1 Helpful Applications and Websites for Safe Prescribing

Websites

Epocrates: http://www.epocrates.com/
LexiComp: http://online.lexi.com/action/home
Pepid: http://www.pepid.com/
Physicians' Desk Reference (PDR): http://www.pdr.net/
UptoDate: http://www.uptodate.com/contents/search

Applications for Tablets, Phones

Centers for Disease Control and Prevention Antibiotic Guidelines
Elsevier Clinical Pharmacology
Epocrates
Pepid
Prescriber's Letter

medication, whereas another patient may not. It is important to note the pertinent side effects for each medication and to ask your patients about presence of symptoms after initiating, stopping, or changing a medication dose. When assessing the risk-to-benefit ratio of a medication, one must consider the severity of the side effects. If a patient started on a new antihypertensive medication has a decreased blood pressure, and therefore improvement in hypertension, but experiences fainting, a decrease in dose or a different medication should be considered.

Allergies

At times, guidelines may suggest a particular drug for a specific ailment. Unfortunately, your patient may have an allergy to that medication or class of drug. It is of critical importance to determine the type of reaction and to document in the patient's chart. Then, selection of an appropriate drug may begin.

In the case of severe allergy, such as anaphylaxis or swelling of the face, these drugs are absolutely contraindicated, but in the case of the patient who experienced vomiting or other similar reactions, the drug may be used again if necessary. The desired choice would be to use an alternate medication that is just as effective. For example, a patient with pyelonephritis who is allergic to penicillin can benefit from a fluoroquinolone instead.

Hepatic and Renal Function

Many drugs are metabolized and eliminated by the liver and kidneys. If these systems are impaired, this can lead to increased adverse effects and possible medication overdose. Frequently, drugs have special decreased doses or different dosing schedules for patients with hepatic or renal impairment. This is known as *hepatic dosing* or *renal dosing*. Despite the known safety of decreasing doses in some drugs, if there is a different option available, it is prudent to choose a different medication. For example, morphine sulfate is highly metabolized by the kidneys. For patients with renal impairment, morphine can be used to treat pain, but the better choice would be fentanyl because fentanyl does not require a dose reduction in patients with renal impairment. Although some drugs are safe to give or can be used with caution in patients with hepatic or renal dysfunction, other drugs are contraindicated in these patients and must be avoided at all costs.

Need for Monitoring

Some drugs require frequent monitoring at initiation or throughout the duration of treatment. Examples of these medications include warfarin, lithium, opioids, and immunosuppressive therapies (tacrolimus, sirolimus). When levels of these drugs are not within therapeutic range, serious patient harm can occur. If a patient does not have the ability to attend frequent laboratory appointments, cannot take their medications reliably, or is not easily reachable by phone or electronically, it may be best to try and avoid these medications if possible.

Special Populations

Populations that deserve special mention when thinking about medications include pregnant or nursing mothers and older adults. These populations are addressed in depth in Unit III, Drug Therapy Across the Life Span. In addition, Life Span Tables are present in many of the chapters throughout the text to alert you to special considerations.

PRESCRIPTIONS

Necessities

When writing any prescription, there are key elements that must be present to compose a complete prescription. An example of a common template for a written prescription is provided in Fig. 2.1. These elements include the following:

- Prescriber name, license number, and contact information

UNIVERSITY CLINIC
Robert Smith, FNP-BC
1777 E. 17th Avenue
Las Vegas, CO 87777
Phone: 777-777-7777 Fax: 777-777-7778

Patient Name: _____ Date: _____
Allergies: _____
Medical Record#: Date of Birth: _____
Medication: _____ Strength: _____ Quantity:
Directions for Use: 0 DAW

Indication for use: Refills: _____
Prescriber Signature: _____ DEA#
License# _____ NPI # _____
Contact #/Pager # _____

Fig. 2.1 Common Example of a Written Prescription. *DAW,* dispense as written; *DEA,* U.S. Drug Enforcement Administration; *NPI,* National Provider Identifier.

- Prescriber U.S. Drug Enforcement Administration (DEA) number, if applicable
- Patient name and date of birth
- Patient allergies
- Name of medication
- Indication of medication (e.g., atenolol for hypertension)
- Medication strength (e.g., 25 mg, 500 mg/mL)
- Dose of medication and frequency (e.g., 12.5 mg once daily)
- Number of tablets or capsules to dispense
- Number of refills
- If using an electronic medical record (EMR) to complete prescriptions, many of these elements will be mandatory for the provider, although many will already be completed by the EMR, including prescriber name and contact information. It is important to note the indication for the medication because many drugs are used for more than one purpose. This allows for the patient as well as other providers to understand your intent for prescribing this particular drug.

Types of Prescriptions

Telephone

A common and convenient way to create a new prescription or prescription refill is by telephone. A prescription can be called in to a pharmacy by you or a specified designee. This is often done by leaving a message with the correct information. Although this is a different way of prescribing, the necessities remain the same (see earlier section "Necessities"). Certain medications cannot be prescribed or refilled by telephone. These include medications within the schedule II category. Patients must have a written prescription for these medications. The only exception to this rule is during an emergency. In this case a telephone order can be used for a limited amount of medication, but a written prescription must be presented to the pharmacy within 7 days.

Written

Providers have been writing prescriptions in the United States since the 1700s. Patients even received scripts during Prohibition in the 1920s to purchase alcohol for medicinal use (Fig. 2.2). Interestingly enough, these paper scripts did not look much different than they do nowadays. This is because the required elements for a complete prescription have not changed over the years. Although health care is making the transition to electronic prescriptions, many providers still use written scripts to prescribe medication. Written prescriptions, like telephone calls or electronic scripts, contain all the necessary elements as described earlier in this chapter. Although all the correct prompts for information may be prepopulated on your script, there are still some important points to consider. If you use a script with a different provider name or a generic script, make sure your name and contact information are printed legibly on the paper. Write all prescriptions in ink or indelible pencil. Avoid abbreviations such as U (units), MSO_4 (morphine), or QD (daily) because these can increase errors and are therefore no longer acceptable. For a list of abbreviations to avoid, see Table 2.1.

In addition, never write prescriptions on presigned scripts or presign blank scripts for other providers or staff. Although this may seem like a convenient way to ensure availability to patients at all times, it is ultimately an unsafe practice. Finally, many facilities provide tamper-resistant scripts, and some states require their use, especially in the prevention of substance misuse and abuse. A few tamper-resistant security features include Hidden Message Technology, which appears when the script is copied on a copy machine; Anti-Copy Coin Rub, which appears when rubbed with a coin; and distinctive security backgrounds.

E-Prescribing

With the advent of the EMR, many pharmacies currently have capabilities to accept electronic prescriptions. In fact, CMS provides incentives for using an EMR to prescribe medications. This program, called *Meaningful Use,* is thought to contribute to increased patient safety and improved patient outcomes.

Using an EMR allows the provider to select a specific, patient-selected pharmacy. After the correct medication information is entered, the prescription is automatically sent to the selected pharmacy. This is beneficial because there is direct transmission of information, making error less likely. In addition, the prescription can be ready for the patient when the patient leaves the facility—the patient does not need to drop off the paper script and then wait for a medication fill. Before the advent of two-factor authentication software, limitations to e-prescribing included scheduled medications. Currently, many companies like

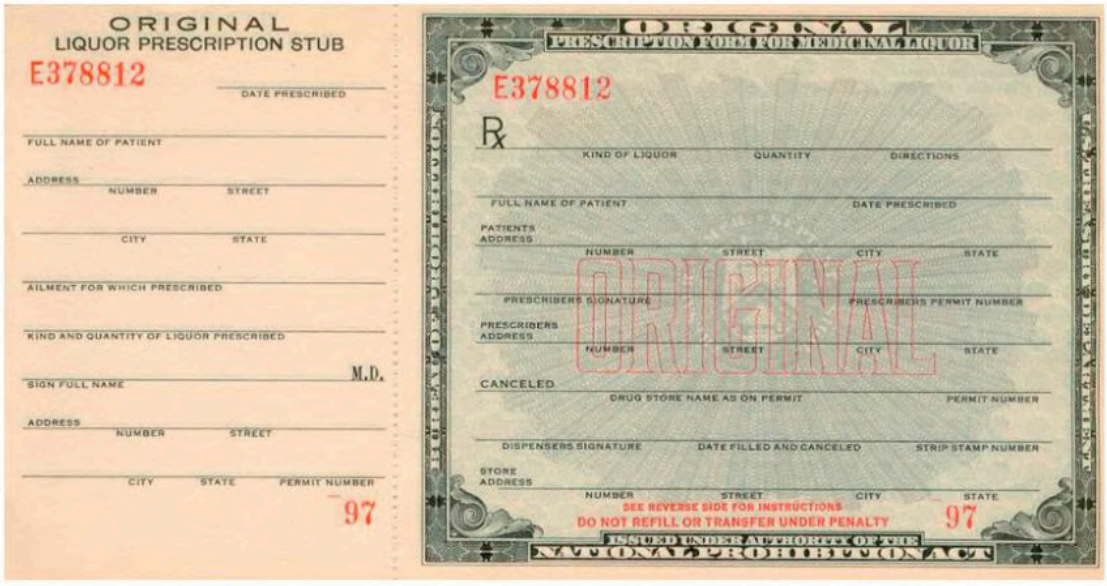

Fig. 2.2 Prohibition Era Prescription for Alcohol.

TABLE 2.1 Abbreviations and Figures to Avoid

Do *Not* Use	Preferred
U	Units
IU	International units
QD	Daily
QOD	Every other day
Trailing zero (X.0 mg)	Never trail (X mg)
Lack of leading zero (.X mg)	Always lead with a zero before a decimal point (0.X mg)
MS, MSO_4, $MgSO_4$	Morphine sulfate, magnesium sulfate
AS, AD, AU	Left ear, right ear, both ears
OS, OD, OU	Left eye, right eye, both eyes

Duo, Nexmo, and OneLogin provide an extra layer of security through use of a smartphone to verify identity at the time of prescribing. These programs are incorporated into the EMR, allowing electronic prescribing of scheduled medications directly to the pharmacy. Unfortunately, many health care organizations still do not have a functional EMR, and many pharmacies still do not have the software capabilities to process these requests. In these cases, paper prescriptions are still necessary.

Refills

There are a few things to consider when refilling a prescription. Questions you should ask yourself include the following:

- Is this a newer medication for this patient?
- Am I changing dose or frequency of the medication?
- Am I adding new medications to their regimen?
- Is the patient having undesired side effects?
- When do I expect to follow up with this patient?
- If the patient is requesting a refill by telephone, when was the last time I saw this patient? Do I need to see the patient again before refill?
- Is this a schedule II medication?

If the answer to any of these questions is "yes," consider a shorter time between refills (1 to 3 months). The exception to this question is with schedule II medications. These are not eligible for refills and must have a new prescription each renewal period. When changing or adding to current medication regimens, it is prudent to follow up with the patient by phone or in person to assess changes. This time can be used to discuss new or increased side effects, check vital signs, obtain laboratory work, or make further adjustments. When a medication, such as warfarin, requires frequent monitoring with drug levels, an even shorter refill allotment is reasonable. If the patient has been maintained on the current dose of a medication for some time and remains stable, it is likely acceptable to continue to refill that medication for a longer time period (e.g., 12 months).

ASSISTANCE

Applications for Tablets and Phones

This textbook will be paramount in your learning, but it may not be convenient to carry around in the clinical setting. Although we encourage you to use this text to the fullest extent, there are many new applications and websites available to assist providers with safe prescribing (Box 2.1). However, it must be noted that all these tools still require common sense and good judgment on the part of the prescriber. As stated previously, one must take into account the individual patient and multiple other factors, including cost, side effects, and medication formularies. An application can assist you with the basic suggestions in dosing and duration, but ultimately there is no substitute for sound practice.

Collaboration

As reflected in this chapter, writing a prescription safely can be complicated. It is strongly encouraged that you use all available resources, including your colleagues. Developing a relationship with your pharmacist can be one of the most helpful and fruitful relationships you cultivate. Because this is their specialty, pharmacists will likely have additional information on formulary and drug interactions, as well as suggestions for adequate medication dosing. In some practices, pharmacists are responsible for medication initiation and titration based on standardized protocols.

Infectious disease (ID) specialists can also be a helpful resource. Choosing an appropriate antimicrobial agent for a specific infectious process is often difficult for a new practitioner. A local ID specialist can provide guidance on resistance patterns, common local microbial flora, and correct doses, as well as on duration of treatment for specific infections.

3

Promoting Positive Outcomes of Drug Therapy

Selecting and prescribing the most appropriate drug (see Chapter 2) is just the first step in providing safe and competent medication therapy. Ensuring positive outcomes requires establishing a medication education plan, monitoring positive and negative patient responses, identifying and addressing issues of nonadherence, and managing the patient's complete medication regimen.

MEDICATION EDUCATION

Probably no other provider action influences the patient's commitment to carry out a medication plan more than medication education. This provides an opportunity to not only explain the importance of the medication but also dispel rumors about medications that often lead to therapy failures. Moreover, education reduces medication errors by empowering patients with accurate information and clear guidelines.

Medication Education Components

There are basic components that should be included when teaching about any new medication. These are (1) medication name, (2) purpose, (3) dosing regimen, (4) administration, (5) adverse effects, (6) any special storage needs, (7) associated laboratory testing, (8) food or drug interactions, and (9) duration of therapy. Each of these is discussed in the following sections.

Medication Name

Patients need to know the name of the medication they are taking. Unfortunately, when taking a medication history, we still have patients who refer to medications by their understood purpose (e.g., "blood pressure pill") rather than by their name. This creates a challenge for the provider who needs to select appropriate therapy. It also increases the risk for medication errors. If we teach patients the medication names, we can avoid this concern.

Patients should be encouraged to keep a list of their medications on their person at all times. Both the generic name and brand (trade) name should be included. This can be especially important for the patient who travels and may be treated by providers unfamiliar with the patient's history.

Purpose

Patients are more likely to participate in activities when they know those activities produce positive outcomes. The same is true of taking medications. Knowing why the medication is prescribed promotes follow-through with the medication plan.

Dosing

The dosing regimen needs to be reviewed with the patient even though it is written on the prescription label. Doing this ensures that the patient understands how to take the medication and provides an opportunity for the patient to ask questions.

It is important to be specific when explaining the dosing regimen. For example, "four times a day" may be interpreted in various ways by different people. Can the medication be taken every 4 hours for four doses, or does it need to be spaced out evenly to every 6 hours? Does "once a day" mean that it can be taken at any time, or is it better to take the medication in the morning or evening hours? Patients need to know what to do if a dose is accidentally skipped. This is also a good time to explain why drugs should be taken exactly as prescribed.

Administration

A common patient concern is whether medication should be taken with or without food. This routine information should be provided for all drugs.

Patients also need to be informed of common administration needs that many of us take for granted. For example, suspensions should be shaken (or rolled, if shaking causes foaming) to equally disperse ingredients before administration.

Finally, some drugs require a special apparatus for administration. Inhaled drugs are a common example. Patients need to see how these are administered and should be able to repeat a demonstration before leaving with a prescription. Many manufacturers provide a device without medication for teaching purposes.

Adverse Effects

Some providers and other health care workers hesitate to discuss a drug's potential adverse effects for fear that doing so will lead to a patient's refusal to take the medication. Although that concern is understandable and the consequences may well be true, patients have a right to know of potential harms that may result from therapy. Therefore providers are ethically obligated to divulge adverse effects and other risks. That said, often the approach used in discussing these can make a difference in how patients view them.

When discussing adverse effects, focus on the adverse effects that are common and avoid undue attention on rare and unanticipated effects. If complex effects such as liver injury or pancytopenia may occur, teach patients the signs and symptoms to report. Let patients know that many adverse effects—most commonly nausea and sedation—are usually temporary and go away with continued medication use. In these discussions, it is also beneficial to emphasize benefits over risks. Patients are often willing to endure short-term adverse effects for long-term health improvement.

Storage

Storage is an important concern for some drugs. For example, some antibiotic suspensions, insulins, and rectal suppositories need to be

refrigerated. Medications such as sublingual nitroglycerin and dabigatran (Pradaxa) need to be stored in their original container to prevent drug breakdown and loss of potency.

Laboratory Testing

Laboratory testing is sometimes necessary to determine whether a medication remains safe and effective. For example, liver enzymes may need to be checked periodically for drugs that can cause liver damage. Serum drug levels may need to be checked when maintaining therapeutic levels is challenging.

Patients need to know if special testing will be needed. They also need to know why the monitoring is necessary because those who understand the purpose are more likely to adhere to testing schedules. We recommend teaching what, when, where, why, and how when giving instructions (Box 3.1).

Food or Drug Interactions

Many medications interact with certain foods or other drugs (including alcohol and other recreational drugs). Patients need to know of any potential interactions and the consequence of those interactions. They also need to know if the problem with interactions can be solved by taking substances further apart or whether they need to avoid an interacting food or drug for the duration of therapy. For example, antacids may be taken with most drugs as long as administration is separated by 2 hours; however, patients taking oral metronidazole must avoid alcohol for the duration of therapy.

Duration of Therapy

It is important to let the patient know if medication therapy is being prescribed for a short time (e.g., antibiotics for an acute infection) or whether ongoing long-term medication therapy is anticipated (e.g., thyroid hormone therapy for hypothyroidism). Failure to recognize the need for prolonged therapy is a common reason patients stop medications prematurely when a prescription runs out.

BOX 3.1 Patient Teaching for Drug Monitoring

When testing is needed for monitoring, include the following when providing patient teaching.

What: What test is needed?
Patients like to know what test is needed. Rather than telling them that a blood test is needed, let them know the type of blood test (e.g., a test of thyroid function or cholesterol levels).

When: When is testing required?
Testing can disrupt normal routines. Patients need to know, in advance, how often testing is needed so that they can make plans.

Where: Where will testing take place?
In some practices, testing takes place at locations other than the primary clinic. Patients who are unfamiliar with the area need directions to the testing site and where to go after arrival.

Why: Why is testing necessary?
Testing is often expensive and disruptive to daily lives. These barriers are common reasons that patients miss appointments. If they understand the need for testing, they are more likely to adhere to testing schedules.

How: How does the patient prepare for testing?
Some tests require special preparation. For example, many blood tests require fasting. If exercise testing is needed, patients should be told to bring comfortable shoes. It is important to let patients know of anything they need to do before arrival.

Written Instructions

Medication information is notoriously easy to forget, especially for patients taking numerous medications. We recommend accompanying all verbal education with written instructions. For those who are unable to read due to literacy or vision problems, video or audio instructions can be used.

The Patient Protection and Affordable Care Act of 2010, Title V, defines health literacy as "the degree to which an individual has the capacity to obtain, communicate, process, and understand basic health information and services to make appropriate health decisions." Low levels of health literacy can impair a patient's ability to understand medication instructions. Best practices in developing written patient education materials abound in the literature. Table 3.1 provides a list of those for which there is greatest consensus. An excellent resource for writing patient education materials is available at http://www.cdc.gov/healthliteracy/pdf/Simply_Put.pdf.

MONITORING

As mentioned in Chapter 2, monitoring is an important consideration in medication therapy. Ongoing monitoring of positive and negative patient responses—and acting on those responses in ways that increase benefit or decrease risk—is essential to ensure optimal outcomes.

There are three primary reasons for drug monitoring: (1) determining therapeutic dosage, (2) evaluating medication adequacy, and (3) identifying adverse effects. Each of these purposes is discussed in the following sections. Table 3.2 provides some common examples of drugs that require periodic laboratory monitoring.

Determining Therapeutic Dosage

Many drugs have a narrow therapeutic index (NTI) (see Chapter 4). Examples include carbamazepine, digoxin, lithium, phenytoin, and theophylline. For these drugs, the difference between an effective dose and a lethal dose is small.

To ensure safety, periodic measurement of serum drug levels is needed when drugs with an NTI are prescribed. This determines whether the drug is in a therapeutic range and also provides an

TABLE 3.1 Best Practices in Developing Written Patient Education Materials

Practice	Rationale
Limit content	Focus on main points. Include only the most important-to-know content.
Place important information first	People tend to remember the first things they read and may become distracted toward the end.
Write in active voice	Active voice is more direct. Passive voice is less dynamic and may be confusing.
Include adequate white space	White space does not contain text or images. White space makes the page feel less cluttered and less overwhelming.
Use meaningful illustrations	Illustrations are a useful way to break up text. Select images or drawings that have a purpose or that reinforce a point in the handout.
Avoid professional terminology	Use common terms in short, simple sentences that patients can easily understand.
Check for readability	Materials should be written at a lower education level that can be understood by most patients. Information for increasing readability is available at http://www.cdc.gov/healthliteracy/pdf/Simply_Put.pdf.

TABLE 3.2 Selected Medications That Require Periodic Laboratory Monitoring

Drug or Drug Category	Laboratory Testing	Reason for Monitoring
ACEIs and ARBs	Potassium	These drugs can cause hyperkalemia.
	Serum creatinine	Renal perfusion is dependent on angiotensin in some patients; increased creatinine may require change in medication.
Amiodarone	Liver function	Hepatotoxicity is an adverse effect.
	Thyroid function	Either hypothyroidism or hyperthyroidism may occur.
	Pulmonary function and chest radiographs	Pulmonary toxicity is not uncommon; effects may be permanent.
Antiseizure drugs	Serum drug levels	Determination of therapeutic dosage is needed. Some have narrow therapeutic index.
Antidiabetic drugs	Serum glucose Hemoglobin A_{1c}	Determination of glucose control is needed.
Digoxin	Digoxin level	This drug has a narrow therapeutic index.
	Serum electrolytes if at risk	Hypokalemia, hypomagnesemia, and hypercalcemia can increase toxicity risk. Hypocalcemia can render the drug ineffective.
Diuretics, potassium-sparing	Serum electrolytes	Hyperkalemia can reach dangerous levels. Hypocalcemia and hypomagnesemia may occur.
Diuretics, thiazide and loop	Serum electrolytes	Hypokalemia, hypomagnesemia, and hyponatremia are common. Thiazide diuretics can cause hypercalcemia; loop diuretics can cause hypocalcemia.
Lithium	CBC	Lithium can cause leukocyte elevation.
	Lithium level	The drug has a narrow therapeutic index.
	Thyroid function	Both hypothyroidism and hyperthyroidism may occur.
	Renal function	Renal damage is a serious adverse effect.
	Serum electrolytes	Nephrogenic diabetes insipidus may occur; hyponatremia can create complications.
Methotrexate	CBC	Pancytopenia, or a decrease of any of the blood cell types, may occur.
	Liver function	Hepatotoxicity is an adverse effect.
	Renal function	Renal toxicity is an adverse effect.
NSAIDs (long-term use)	CBC	Anemia may occur, especially if there is bleeding, which may be occult.
	Serum creatinine	Prostaglandin inhibition may decrease renal perfusion, causing injury.
	Liver function	Rare but serious liver injury has occurred.
Statins	Liver function	Elevations in liver enzymes may be associated with injury.
	Creatine kinase	Creatine kinase can determine whether muscle pain is caused by injury secondary to drug use.
	Lipid panel	Lipids are checked to determine effect.
Thiazolidinediones	Liver function	These drugs are associated with a risk for hepatotoxicity.
Thyroid hormone	TSH, T_4	Monitoring is needed to optimize therapy.
Warfarin	PT/INR	Monitoring is needed to maintain therapeutic range.

ACEI, Angiotensin-converting enzyme inhibitor; *ARB*, angiotensin receptor blocker; *CBC*, complete blood count; *NSAIDs,* nonsteroidal antiinflammatory drugs; *PT/INR*, prothrombin time/international normalized ratio; *T*4, thyroxine *TSH;* thyroid-stimulating hormone.

opportunity for fine-tuning the dosage. If a drug is nearing a toxic level or a subtherapeutic level, the provider will make a dosage adjustment accordingly. How often monitoring is needed varies for each drug. In addition, patient factors such as poor liver or renal function may determine the frequency of drug level monitoring.

For some drugs with an NTI, a therapeutic dosage is determined by means other than the serum drug level. Warfarin is a drug that illustrates this method. Instead of ordering a serum warfarin level, optimal dosing is determined by measures of prothrombin time with international normalized ratio (PT/INR).

Evaluating Medication Adequacy

For some drugs, evaluation of effectiveness can be determined easily. For example, if an analgesic is given, effectiveness is determined by asking the patient to rate the pain on a scale of 0 to 10. Similarly, the adequacy of an antihypertensive medication can be evaluated by checking the patient's blood pressure. However, evaluating medication adequacy is not so simple for some conditions.

Some conditions do not cause obvious signs or symptoms. Hyperlipidemia is a common example; signs and symptoms often do not appear until after decades of accumulated damage have occurred. Other conditions may be manifested by signs and symptoms that are not easily quantifiable. A common example of this condition is hyperglycemia associated with diabetes. Some people display obvious signs and symptoms when hyperglycemic, whereas for others, the evidence is much more subtle. For conditions such as hyperlipidemia and hyperglycemia, laboratory testing offers a precisely quantifiable measure that can be used to gauge the effectiveness of medication therapy. For example, a hemoglobin A_{1c} level can be used to evaluate glucose control, and lipid panels can used to determine the effectiveness of hyperlipidemia management.

Identifying Adverse Effects

One of the most common uses of drug monitoring is that of monitoring for harm. This is a proactive undertaking to identify problems early, before they progress to the point of harm.

Many drugs are potentially dangerous. For these, monitoring depends on the type of potential injury. For example, if a drug can cause liver injury, periodic monitoring of liver enzymes (and possibly other tests of liver function) is needed. If a drug can cause bone marrow suppression, periodic monitoring of a complete blood count to assess for anemia, leukopenia, or thrombocytopenia is warranted. In addition, baseline laboratory studies are done before initiating therapy.

ADHERENCE

Medication nonadherence costs the U.S. health care system approximately $290 billion each year. It is often directly responsible for disease exacerbations, avoidable hospitalizations, transitioning to long-term (i.e., "nursing home") care, and premature deaths.

Medication adherence can be defined as the extent to which patients take their medications as prescribed by the provider and agreed to by the patient.[a] The patient who adheres to the agreed-on medication regimen takes the medication in the prescribed dose at the prescribed frequency for the length of time indicated.

To determine the underlying reasons behind nonadherence, the National Community Pharmacists Association (NCPA) surveyed a random sample of 1020 adults aged 40 years or older with long-term medical conditions for which they were prescribed medications. Their findings were released as *Medication Adherence in America: A National Report Card* (available at http://www.ncpa.co/adherence/AdherenceReportCard_Full.pdf). The NCPA report identifies six nonadherent behaviors. They are, in the percentage of frequency, as follows:

- Missed a dose (57%)
- Forgot to take a dose (30%)
- Did not refill the medication in time (28%)
- Took a lower than prescribed dose (22%)
- Did not refill the medication (20%)
- Stopped taking the medication (14%)

The reasons given by patients to explain their nonadherence provide additional insight. Again, in the frequency of occurrence, they are as follows:

- Forgot to take it (42%)
- Ran out (34%)
- Was away from home (27%)
- Was trying to save money (22%)
- Didn't like the side effects (21%)
- Was too busy (17%)
- The medicine wasn't working (17%)
- Didn't believe the medicine was necessary (16%)
- Didn't like taking the medicine (12%)

These documents can offer valuable insight for the health care provider. Moreover, they beg the question, "What could the provider have done differently to address issues of nonadherence proactively?"

In examining these, five primary patterns emerge. These are (1) forgetfulness, (2) lack of planning, (3) cost, (4) dissatisfaction, and (5) altered dosing. An honest and open discussion that respects both the patient and provider perspectives can be an important facilitator to promoting positive outcomes. Individualized solutions that address the specific patient's concerns are those most likely to be successful (Table 3.3). Finally, provide positive feedback that reinforces how adherence has resulted in improved outcomes or health maintenance.

[a]The addition of "agreed to by the patient" distinguishes the definition of medication adherence from medication compliance. The concept of medication compliance has fallen out of favor because it views the provider from the perspective of an authoritarian who dictates treatment rather than a provider who makes decisions that consider the patient's preferences and values.

MANAGING MEDICATION THERAPY

In addition to the medication review undertaken at each patient encounter, a more comprehensive and deliberate review is needed periodically (at least annually). This review should be approached with the intent purpose of determining whether there are better options for

TABLE 3.3 Interventions to Address Nonadherence

Forgetfulness	Schedule medications to align with daily activities to establish habits.
	Use memory aids such as medication organizers.
	Employ digital reminder apps on electronic devices.
	Develop a personalized medication administration record for home use.
	Simplify medication regimens by prescribing combination drugs.
	Use once-a-day formulations when feasible.
Lack of planning	Have the patient use a pharmacy that sends reminder messages regarding medication refills.
	Have the patient use a pharmacy that offers delivery services.
	Reduce the need to refill frequently by writing 90-day prescriptions.
Cost	Prescribe generic drugs, drugs on formularies, or drugs that are part of a discount pharmacy program to reduce out-of-pocket costs.
	Assist the patient in enrolling in prescription assistance programs (PAPs) when an expensive drug is needed[a] (see Table 3.4).
Dissatisfaction	Discuss medication concerns at each encounter.
	Determine if the problem can be addressed by simple interventions (e.g., taking medications with food to reduce nausea and gastrointestinal distress or changing to a sustained-release drug to address problems with inconvenient dosing).
	Explore consequences of not taking the drug and whether the patient is willing to assume those risks.
Altered dosing	Review drugs at each encounter and ask whether they are taken as prescribed.
	Identify the reasons why doses are altered and address those reasons specifically.
	Explain that drugs must reach a therapeutic level to be effective. A subtherapeutic dose is no better than no dose at all!
	Discuss dangers of low doses (e.g., for some antimicrobial drugs, subtherapeutic levels may cause harm if the bacteria develop resistance).
	Explain that increasing drug dosage can be dangerous and may increase adverse effects.

[a]Warn patients to beware of discount cards that are not affiliated with known reputable organizations. Unfortunately, some criminals use applications for fake cards for illegal purposes.

TABLE 3.4 Patient Assistance Programs

Pharmaceutical Patient Assistance Programs

Allergan	https://www.allergan.com/Home/patient-assistance-programs
AstraZeneca	http://www.astrazeneca-us.com/medicines/help-affording-your-medicines
Boehringer Ingelheim	https://www.boehringer-ingelheim.us/our-responsibility/patient-assistance-program
Johnson & Johnson	http://www.jjpaf.org
Merck	http://www.merckhelps.com
Novartis	http://www.patientassistancenow.com
Pfizer	http://www.pfizer.com/health/financial_assistance_programs/patient_assistance_programs
Takeda	https://www.takeda.com/en-us/what-we-do/patient-services/

Government Programs

Medicare	https://www.medicare.gov/pharmaceutical-assistance-program
State-run programs	http://www.ncsl.org/research/health/state-pharmaceutical-assistance-programs.aspx

Nonprofit Organizations

National Council on Aging	https://www.ncoa.org/age-well-planner/resource/how-to-get-help-with-your-prescription-drug-costs
NeedyMeds	http://www.needymeds.org
Patient Help Network	http://www.patienthelpnetwork.org/
RxAssist	http://www.rxassist.org
RxHope	https://www.rxhope.com/Patient/MedSearchHome.aspx
RxOutreach Online Nonprofit Pharmacy	https://rxoutreach.org

medication therapy. Inherent questions that must be asked about each drug include the following:

- Is each medication accomplishing its intended purpose?
- Is each medication still necessary?
  - Has the patient's condition changed?
  - Do adverse effects or risks outweigh the benefits that some drugs provide?
  - What would happen if some medications were no longer prescribed?
- What problems does each medication create for the patient?
  - Is a medication problem amplified by other drugs the patient is taking?
  - If a medication is necessary but problematic, are drugs with fewer adverse effects available?
- If polypharmacy is an issue, are there ways to decrease the number of medications?
  - Will a combination drug simplify management?
  - Is a single drug available (and desirable) for management of two different conditions?

Ideally, these reviews should be carried out in collaboration with the patient or patient's family so that nothing is overlooked. Medication regimens can then be optimized to eliminate unnecessary drugs, add new drugs, if necessary, and ultimately improve patient satisfaction with care.

SUMMARY

We have examined four opportunities to promote positive outcomes in drug therapy. Patients need adequate drug education to take drugs correctly and to avoid complications associated with therapy. Monitoring provides a method of ensuring safe and effective therapy. Promoting adherence, by addressing common causes of nonadherence proactively, can ensure ongoing therapy without interruption. Finally, scheduled medication reviews with the intent to optimize medication regimens, based on patient experiences and needs, can help promote positive outcomes.

4

Pharmacokinetics, Pharmacodynamics, and Drug Interactions

PHARMACOKINETICS

Pharmacodynamics is defined as the study of the biochemical and physiologic effects of drugs on the body and the molecular mechanisms by which those effects are produced. In essence, pharmacokinetics is the study of drug movement throughout the body. There are four basic pharmacokinetic processes: absorption, distribution, metabolism, and excretion (Fig. 4.1). *Absorption* is the drug's movement from its site of administration into the blood. *Distribution* is the drug's movement from the blood to the interstitial space of tissues and from there into cells. *Metabolism* (biotransformation) is the enzymatically mediated alteration of drug structure. *Excretion* is the movement of drugs and their metabolites out of the body. The combination of metabolism and excretion is called *elimination*. The four pharmacokinetic processes, acting in concert, determine the concentration of a drug at its sites of action.

By applying knowledge of pharmacokinetics to drug therapy, we can help maximize beneficial effects and minimize harm. Recall that the intensity of the response to a drug is directly related to the concentration of the drug at its site of action. To maximize beneficial effects, a drug must achieve concentrations that are high enough to elicit desired responses; to minimize harm, we must avoid concentrations that are too high. This balance is achieved by selecting the most appropriate route, dosage, and dosing schedule.

PASSAGE OF DRUGS ACROSS MEMBRANES

All four phases of pharmacokinetics—absorption, distribution, metabolism, and excretion—involve drug movement. To move throughout the body, drugs must cross membranes. Drugs cross membranes as they pass from the site of administration into the bloodstream and, subsequently, as they leave the vascular system to reach the site of action. In addition, drugs must cross membranes to undergo metabolism and excretion. Accordingly, the factors that determine the passage of drugs across biologic membranes have a profound influence on all aspects of pharmacokinetics.

Biologic membranes are composed of layers of individual cells. The cells composing most membranes are close to one another—so close, in fact, that drugs must usually pass *through* cells, rather than between them, to cross the membrane. Hence the ability of a drug to cross a biologic membrane is determined primarily by its ability to pass through single cells.

Three Ways to Cross a Cell Membrane

The three most important ways by which drugs cross cell membranes are (1) passage through channels or pores, (2) passage with the aid of a transport system, and (3) direct penetration of the membrane. Of the three, direct penetration of the membrane is most common.

Channels and Pores

Few drugs cross membranes through channels or pores. The channels in membranes are extremely small and are specific for certain molecules. Consequently, only the smallest of compounds, such as potassium and sodium, can pass through these channels and then only if the channel is the right one.

Transport Systems

Transport systems are carriers that can move drugs from one side of the cell membrane to the other side. All transport systems are selective. Whether a transporter will carry a particular drug depends on the drug's structure.

A number of drugs could not reach intracellular sites of action without a transport system to move them across the cell membrane. One transporter, known as *P-glycoprotein* (PGP) or *multidrug transporter protein,* deserves special mention. PGP is a transmembrane protein that transports a wide variety of drugs *out* of cells.

Direct Penetration of the Membrane

For most drugs, movement throughout the body is dependent on the ability to penetrate membranes directly because (1) most drugs are too large to pass through channels or pores and (2) most drugs lack transport systems to help them cross all of the membranes that separate them from their sites of action, metabolism, and excretion.

A general rule in chemistry states that "like dissolves like." Membranes are composed primarily of lipids; therefore, to directly penetrate membranes, a drug must be *lipid soluble* (lipophilic).

POLAR MOLECULES AND IONS

Certain kinds of molecules are *not* lipid soluble and therefore cannot penetrate membranes. This group consists of *polar molecules* and *ions.*

Polar Molecules

Polar molecules are molecules that have no *net* charge; however, they have an uneven *distribution* of electrical charge. That is, positive and

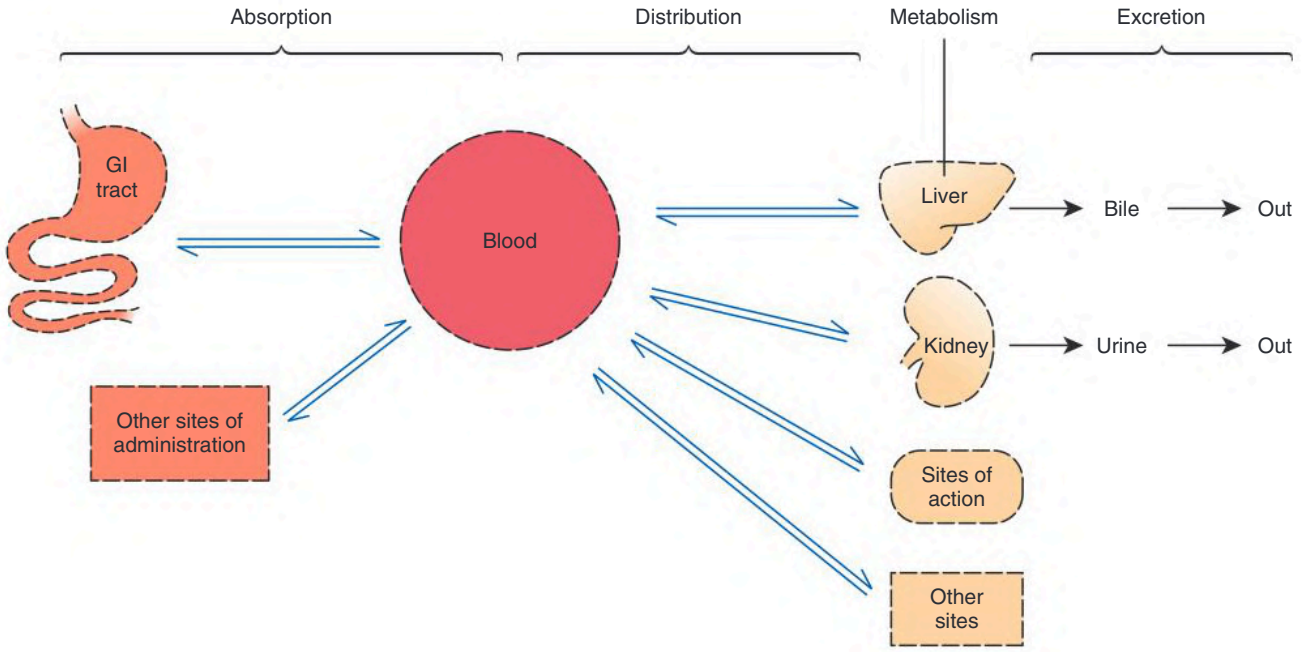

Fig. 4.1 The Four Basic Pharmacokinetic Processes. Dotted lines represent membranes that must be crossed as drugs move throughout the body. *GI*, Gastrointestinal.

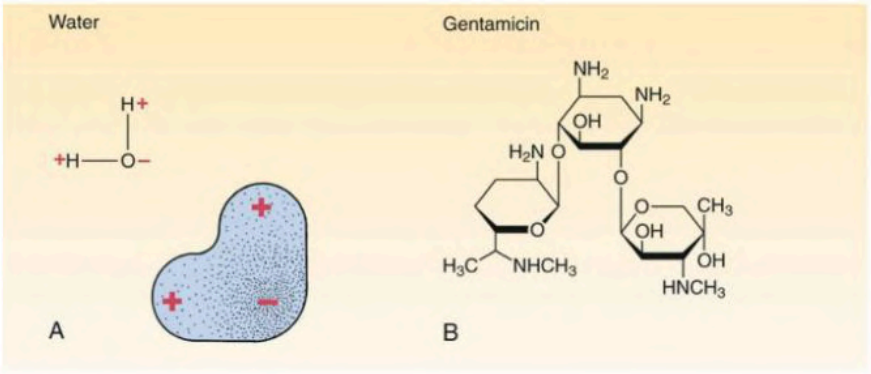

Fig. 4.2 Polar Molecules. (A) Stippling shows the distribution of electrons within the water molecule. As indicated at the lower right, water's electrons spend more time near the oxygen atom than near the hydrogen atoms, making the area near the oxygen atom somewhat negative and the area near the hydrogen atoms more positive. (B) Gentamicin is a polar drug. The 2-OH groups of gentamicin attract electrons, thereby causing the area around these groups to be more negative than the rest of the molecule.

negative charges within the molecule tend to congregate separately from one another. Water is the classic example. As depicted in Fig. 4.2, the electrons (negative charges) in the water molecule spend more time in the vicinity of the oxygen atom than in the vicinity of the two hydrogen atoms. As a result, the area around the oxygen atom tends to be negatively charged, whereas the area around the hydrogen atoms tends to be positively charged. In accord with the "like dissolves like" rule, polar molecules will dissolve in *polar* solvents (such as water) but not in *nonpolar* solvents (such as lipids).

Ions

Ions are defined as molecules that have a *net electrical charge* (either positive or negative). Except for tiny molecules, *ions are unable to cross membranes;* therefore they must become nonionized to cross from one side to the other. Many drugs are either weak organic acids or weak organic bases, which can exist in charged and uncharged forms. Whether a weak acid or base carries an electrical charge is determined by the pH of the surrounding medium. Acids tend to ionize in basic (alkaline) media, whereas bases tend to ionize in acidic media. Therefore drugs that are weak acids are best absorbed in an acidic environment such as gastric acid because they remain in a nonionized form. When aspirin molecules pass from the stomach and proximal small intestine into the more distal small intestine, where the environment is relatively alkaline, more of the molecules change to their ionized form. As a result, absorption of aspirin from the more distal intestine is impeded.

pH Partitioning (Ion Trapping)

Because the ionization of drugs is pH dependent, when the pH of the fluid on one side of a membrane differs from the pH of the fluid on the other side, drug molecules tend to accumulate on the side where the pH most favors their ionization. Accordingly, because acidic drugs tend to ionize in basic media and because basic drugs tend to ionize in

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