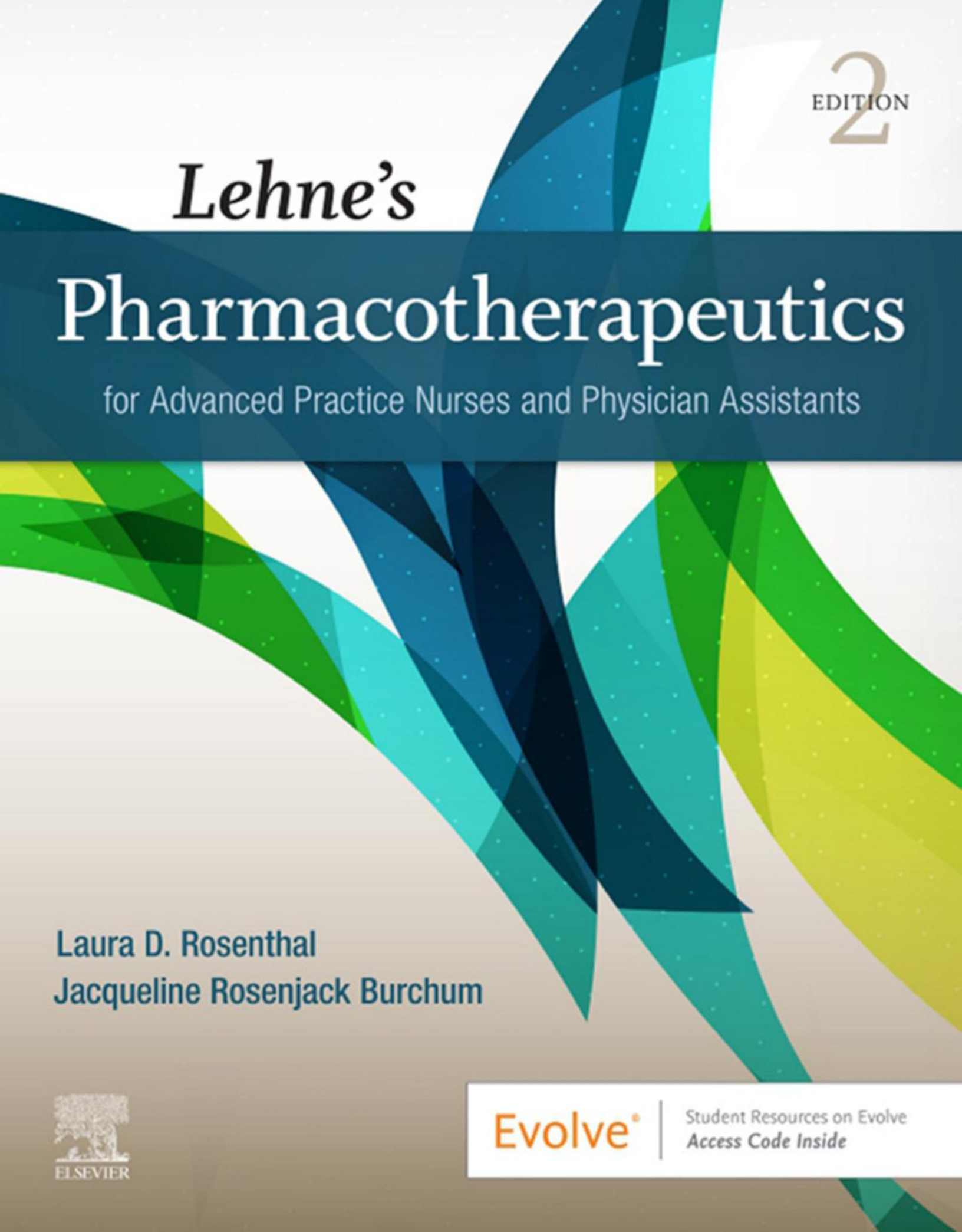
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Lehne's
Pharmacotherapeutics
for Advanced Practice Nurses and Physician Assistants
Laura D. Rosenthal
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Lehne's Pharmacotherapeutics

for Advanced Practice Nurses and Physician Assistants

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St. Louis, Missouri 63043

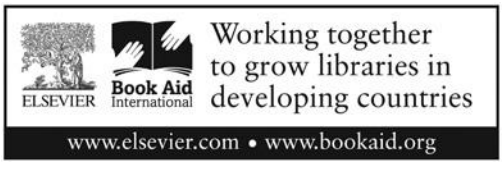
LEHNE'S PHARMACOTHERAPEUTICS FOR ADVANCED PRACTICE NURSES AND PHYSICIAN ASSISTANTS, SECOND EDITION
ISBN: 978-0-323-55495-4

Library of Congress Control Number: 2019940236

Executive Content Strategist: Lee Henderson
Senior Content Development Manager: Luke Held
Senior Content Development Specialist: Jennifer Wade
Publishing Services Manager: Julie Eddy
Senior Project Manager: Rachel E. McMullen
Design Direction: Renee Duenow

Printed in China

Last digit is the print number: 9 8 7 6 5 4 3 2 1



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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ACKNOWLEDGMENTS

We would like to acknowledge the support of our colleagues at Elsevier, including Lee Henderson, Executive Content Strategist; Jennifer Wade, Senior Content Development Specialist; and Rachel McMullen, Senior Project Manager. Finally, we would like to acknowledge the foundational work by Richard A. Lehne. His dedication to the Lehne Pharmacology series made this text possible.

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Pharmacology and pharmacotherapeutics pervade all phases of advanced 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 texts have stressed *memorizing* rather than *understanding*. In this text, the guiding principle is to establish further understanding of drugs and their use in patient care.

This text has two major objectives: to help you, the advanced practice student, 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 70).

REVIEWING PHYSIOLOGY AND PATHOPHYSIOLOGY

To understand the actions of a drug, it is useful to understand the biologic 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 a 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 text, 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. Not only is this approach more efficient than the traditional approach, it is 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 when clinical trials reveal new benefits or new risks of older drugs, the guidelines change—and so we have to work hard to keep this book current. Despite our best efforts, the book and clinical reality may not always agree. Some treatments discussed here will be considered inappropriate before the second edition comes out. Furthermore, in areas where controversy exists, the treatments discussed here may be considered inappropriate by some clinicians right now.

SPECIAL FEATURES

- **Summary of Key Prescribing Considerations:** This summary provides guidance for safe prescribing practices and includes 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.
- **Patient-Centered Care Across the Life Span:** Tables 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 for the first edition are available online and include a **Test Bank**, a **PowerPoint Collection**, and an **Image Collection.**

STUDENT RESOURCES

- New online student resources include one case study per textbook section.

WAYS TO USE THIS TEXTBOOK

Thanks to its focus on essentials, this text 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) using standard print for essential information and small print for secondary information, (3) limiting discussion of adverse effects and drug interactions to information that matters most, and (4) 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 VI Drugs for Pain

UNIT VIII Substance Use Disorders

UNIT IX Drugs That Affect the Heart, Blood Vessels, Blood, and Blood Volume

UNIT X Drugs for Endocrine Disorders

UNIT XIX Cancer Therapy

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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 (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/download/28349 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 quasi-full prescriptive authority. Indeed, some have referred to this as full prescriptive authority; however, the issue of being affiliated to 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 APRNs. Table 1.2 provides prescriptive authority status for PAs. 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* 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: Focus on Scope of Practice.* After noting problems with the "patchwork of state regulations," they wrote:

> *The federal government 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*

TABLE 1.1 Advanced Practice Registered Nurse Prescriptive Authority by State

State	Authorized to Prescribe	Scheduled Drugs	Type of Practice (Independent or Physician Collaboration Required)
AL	CNM, CNP	III–V, limited II	Collaborative
AK	CNM, CNP, CNS, CRNA	II–V	Independent
AZ	CNM, CNP	II–V	Independent
AR	CNM, CNP, CNS, CRNA	III–V	Collaborative
CA	CNM, CNP	II–V	Collaborative
CO	CNM, CNP, CNS, CRNA	II–V	Independent
CT	CNM, CNP, CRNA	II–V	Collaborative
DE	CNM, CNP, CNS, CRNA	II–V	Collaborative
FL	CNM, CNP, CRNA	III–V	Collaborative
GA	CNM, CNP, CNS, CRNA	III–V	Collaborative
HI	CNM, CNP, CNS, CRNA	II–V	Independent
ID	CNM, CNP, CNS, CRNA	II–V	Independent
IL	CNM, CNP, CNS, CRNA	III–V	Collaborative
IN	CNM, CNP, CNS	II–V (within limits)	Collaborative
IA	CNM, CNP, CNS, CRNA	II–V	Independent
KS	CNM, CNP, CNS	II–V	Collaborative
KY	CNM, CNP, CNS, CRNA	II–V	Collaborative
LA	CNM, CNP, CNS, CRNA	II–V	Collaborative
ME	CNM, CNP	II–V	Independent
MD	CNM, CNP	II–V	Independent
MA	CNM, CNP, CNS, CRNA	II–V	Collaborative: CNP, CNS, CRNA Independent: CNM
MI	CNM, CNP, CRNA	III–V	Collaborative
MN	CNM, CNP, CNS, CRNA	II–V	Independent
MS	CNM, CNP, CRNA	II–V	Collaborative
MO	CNM, CNP, CNS, CRNA	III–V	Collaborative
MT	CNM, CNP, CNS, CRNA	II–V	Independent
NE	CNM, CNP, CRNA	II–V	Collaborative
NV	CNM, CNP, CNS	III–V	Independent
NH	CNM, CNP, CNS, CRNA	II–V	Independent
NJ	CNP, CNS, CRNA	II–V	Collaborative
NM	CNP, CNS, CRNA	II–V	Independent
NY	CNM, CNP	II–V	Independent
NC	CNM, CNP	II–V	Collaborative
ND	CNM, CNP, CNS, CRNA	II–V	Independent
OH	CNM, CNP, CNS	II–V	Collaborative
OK	CNM, CNP, CNS	III–V	Collaborative
OR	CNM, CNP, CNS, CRNA	II–V	Independent
PA	CNP	II–V	Collaborative
RI	CNP, CNS, CRNA	II–V	Independent
SC	CNM, CNP, CNS	III–V	Collaborative
SD	CNM, CNP	II–V	Independent
TN	CNM, CNP, CNS, CRNA	II–V	Collaborative
TX	CNM, CNP, CNS, CRNA	III–V	Collaborative
UT	CNM, CNP, CNS, CRNA	III–V, II if collaborative practice	Independent
VT	CNM, CNP, CNS, CRNA	II–V	Collaborative
VA	CNM, CNP, CNS	II–V	Collaborative
WA	CNM, CNP, CRNA	II–V	Independent
WV	CNM, CNP, CNS, CRNA	III–V	Collaborative
WI	CNM, CNP, CNS, CRNA	II–V	Collaborative
WY	CNM, CNP, CNS, CRNA	II–V	Independent

CNM, Certified nurse midwife; *CNP*, certified nurse practitioner; *CNS*, clinical nurse specialist; *CRNA*, certified registered nurse anesthetist.
Source: State Boards of Nursing; November 2018.

TABLE 1.2 Physician Assistants Prescriptive Authority by State

State	Scheduled Drugs	Required Physician Affiliation for Practice
AL	II–V	Supervisory
AK	II–V	Collaborative
AZ	II–V	Supervisory
AR	III–V	Supervisory
CA	II–V	Supervisory
CO	II–V	Supervisory
CT	II–V	Supervisory
DE	II–V	Supervisory
FL	II–V	Supervisory
GA	III–V	Supervisory
HI	III–V	Supervisory
ID	II–V	Supervisory
IL	II–V	Collaborative
IN	II–V	Supervisory
IA	II–V	Supervisory
KS	II–V	Supervisory
KY	No	Supervisory
LA	II–V	Supervisory
ME	II–V	Supervisory
MD	II–V	Supervisory
MA	II–V	Supervisory
MI	II–V	Participating[a]
MN	II–V	Supervisory
MS	II–V	Supervisory
MO	III–V	Supervisory
MT	III–V	Supervisory
NE	II–V	Supervisory
NV	II–V	Collaborative
NH	II–V	Supervisory
NJ	II–V	Supervisory
NM	II–V	Varies according to practice
NY	II–V	Supervisory
NC	II–V	Supervisory
ND	II–V	Supervisory
OH	II–V	Supervisory
OK	II–V	Supervisory
OR	II–V	Supervisory
PA	II–V	Supervisory
RI	II–V	Supervisory
SC	II–V	Supervisory
SD	II–V	Supervisory
TN	II–V	Supervisory
TX	III–V	Supervisory
UT	II–V	Supervisory
VT	II–V	Supervisory
VA	II–V	Supervisory
WA	II–V	Supervisory
WV	III–V	Collaborative
WI	II–V	Supervisory
WY	II–V	Supervisory

[a]Physician assistants (PAs) are required to have a PA–physician relationship that is detailed in a written practice agreement.
Source: American Medical Association. Physician assistant scope of practice; 2018. Available at: https://www.ama-assn.org/sites/ama-assn.org/files/corp/media-browser/public/arc-public/state-law-physician-assistant-scope-practice.pdf.
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education and training. (http://www.nationalacademies.org/hmd/~/media/Files/Report%20Files/2010/The-Future-of-Nursing/Nursing%20Scope%20of%20Practice%202010%20Brief.pdf)

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 2010, the Association of American Medical Colleges commissioned a report projecting the future of the physician workforce. The report, *The Complexities of Physician Supply and Demand: Projections from 2013 to 2025,* was released in 2015. Several of the key findings have important implications for nonphysician providers.

- By 2025, the shortage of physicians will range between 46,100 and 90,400. In primary care alone, a 12,500 to 31,100 physician shortage is anticipated. *(The lower numbers on these ranges reflect an increase in APRNs and PAs used to help offset physician shortages.)*
- As the Affordable Care Act is fully implemented, the demand for provider coverage will increase.

These findings echo the dire circumstances reported in the 2013 Department of Health and Human Services report, *Projecting the Supply and Demand for Primary Care Practitioners through 2020,* which concluded that full utilization of nurse practitioners and PAs can reduce the physician shortage.

In this scenario, 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 afford 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 the following box 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 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 very 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 other 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 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
- 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

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. *DEA*, U.S. Drug Enforcement Administration, *DAW*, dispense as written; *NPI*, National Provider Identifier.

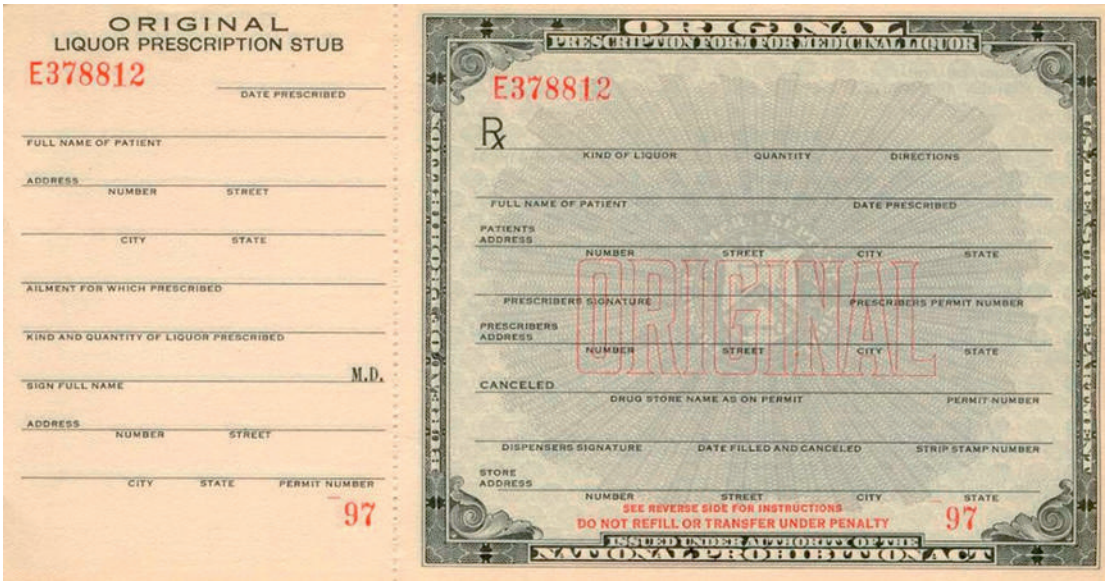

Fig. 2.2 Prohibition Era Prescription for Alcohol.

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. To learn more about these features, visit http://rxsecurityfeatures.com/.

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

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. Prior to the advent of Two-Factor Authentication software, limitations to e-prescribing included scheduled medications. Currently, many companies like 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.

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

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 not only provides an opportunity to explain the importance of the medication but also allows the provider to 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 the 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. From the patient perspective, knowing the generic name empowers the patient to catch medication errors in the event that two different providers prescribe the same generic drug under different brand names.

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 the reason the medication is prescribed propels the patient to follow through with the medication plan because the patient is aware that this action helps achieve the therapeutic goal.

Dosing

The dosing regimen, including the drug quantity and number of tablets or millimeters per dose, 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 it is 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 "dummy" device for teaching purposes.

Adverse Effects

Some providers and other health care workers hesitate to discuss a drug's potential adverse effects. Some fear that doing so will lead to a patient's refusal to take the medications. 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.

You probably know patients who worry about taking drugs when the product labeling (i.e., package insert) lists dozens of adverse effects. Patients may not know that, for most drugs, most adverse effects occur in less than 1% to 2% of those taking the drug. Most patients are unaware that the long list of adverse effects represents all effects reported during clinical trials, regardless of whether a direct association to the drug is known. Furthermore, labeling does not mention that sometimes the incidence of adverse effects in the placebo group is similarly high. For example, in clinical trials of lovastatin, 1.8% of subjects taking 40 mg reported myalgias; however, 1.7% of subjects taking a placebo also reported myalgias.

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 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.

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.

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 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 prior to arrival.

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.
Anticonvulsants	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	The drugs have a narrow therapeutic index.
	Serum electrolytes if at risk	Hypokalemia, hypomagnesemia, and hypocalcemia can increase toxicity risk.
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; *TSH*, thyroid-stimulating hormone; *T_4*, thyroxine.

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 not only determines whether the drug is in a therapeutic range but also provides an opportunity for fine-tuning of 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.

In 2013, the National Community Pharmacists Association (NCPA) released *Medication Adherence in America: A National Report Card* (available at http://www.ncpa.co/adherence/AdherenceReportCard_Full.pdf with yearly progress reports at http://www.ncpanet.org/solutions/adherence-simplify-my-meds). 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%)

[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.

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.

Forgetfulness

The most common reason cited for nonadherence was that the patient simply forgot to take the medication. Studies have demonstrated that medications are easier to remember if they are aligned with common daily activities. For example, morning medications may be taken on first arising (if they should be taken on an empty stomach) or with breakfast (if they should be taken with food). Doing this establishes habits, which are more difficult to forget.

Several memory aids are available to help patients remember to take their medications. Drug organizers are probably the most common tool used. If these are filled at the beginning of each week, the patient can tell at a glance if medications have been taken on any given day.

Numerous apps are also available for various electronic devices. These can be programmed to alarm or deliver a verbal message when it is time to take a drug. Similarly, digital assistances (e.g., Amazon's Alexa and Google Assistant) can be programmed to alert patients when it is time to take their medications.

Some patients have found that medication administration records (MARs), similar to MARs used by nurses in hospitals, can be helpful. An advantage of personalized MARs is the ability to tailor them to meet patient's vision and literacy needs.

Lack of Planning

Aligned closely with forgetfulness is the lack of planning. In this category, we include those statements aligned with failure to refill medications whether because the patient was too busy, away from home, or ran out for other reasons.

Most pharmacies offer reminder notices, either by email or automated phone calls, as part of their regular services. If being "too busy" is a concern, a pharmacy that offers a home delivery service or a mail delivery service is a viable solution.

Cost

As mentioned in Chapter 2, costs should be considered initially when selecting an appropriate drug. When possible, use of generic drugs, drugs on formulary, or drugs that are a part of a discount pharmacy program can reduce out of pocket costs. Sometimes, however, there are no adequate substitutions for a necessary but expensive drug. Fortunately, prescription assistance programs (PAPs), also called *patient assistance programs* and *pharmaceutical assistance programs*, are widely available. These offer steeply discounted drugs for those who meet eligibility requirements.

There are three sources for PAPs: pharmaceutical companies, government-run programs, and nonprofit organizations. Table 3.3 offers a program sampling. If you do not find what you need here, your likely best resource for reliable information is a local pharmacist. 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.

Dissatisfaction

The issue of dissatisfaction as a reason for nonadherence highlights the need to identify what medications are taken and to discuss any concerns

TABLE 3.3 Patient Assistance Programs

Pharmaceutical Patient Assistance Programs	
Allergan	http://www.allergan.com/responsibility/patient-resources/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	http://www.takeda.us/responsibility/patient_assistance_program.aspx
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/economic-security/benefits/prescriptions/lis-extrahelp
NeedyMeds	http://www.needymeds.org
Partnership for Prescription Assistance	https://www.pparx.org
RxAssist	http://www.rxassist.org
RxHope	https://www.rxhope.com/Patient/MedSearchHome.aspx
RxOutreach	https://rxoutreach.org

with the patient at each encounter. It is essential to uncover the reason for dissatisfaction (e.g., adverse effects, inconvenient dosing, or a perception that a drug is ineffective). Often the problem can be easily addressed by simple interventions. For example, taking medications with food can reduce adverse effects of nausea and gastrointestinal distress in many instances. Changing to a sustained-release drug may be all that is necessary to address problems with inconvenient dosing.

If the patient believes a drug is ineffective, it becomes important to discuss patient expectations of drug therapy and what can be realistically achieved. For some conditions (e.g., obesity), change may come slowly. For others (e.g., hypertension), the medication may cause the patient to feel worse without a perceived benefit. If the drug is truly an important one, this may be a good time to explore with the patient any consequences of not taking the drug and whether the patient is willing to assume those risks. In some instances the patient may decide to assume those risks rather than to take the medication. It is within the patient's right to do so.

Altered Dosing

It is concerning that more than 20% of patients in the NCPA report took lower than the prescribed dose. The reasons were not made clear; however, the consequence is this, because a drug must reach a therapeutic level to be effective, a subtherapeutic dose is no better than no dose at all! Furthermore, in the case of certain antimicrobial drugs, subtherapeutic levels may cause harm if the bacteria develop resistance as a result.

This finding emphasizes the necessity of not only reviewing which medications are taken at each encounter but also asking whether the medications are taken as prescribed. If dosing is altered, it is imperative to determine how and why, and then to educate the patient regarding how alterations in dosing affect outcomes.

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 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

Pharmacokinetics is the study of drug movement throughout the body.[a] 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.

[a]Fundamental pharmacologic concepts are typically covered in undergraduate courses; however, experience has demonstrated that a refresher in the basic principles of pharmacokinetics, pharmacodynamics, and drug interactions is usually helpful. Because it is a refresher, the information in this chapter is relatively brief.

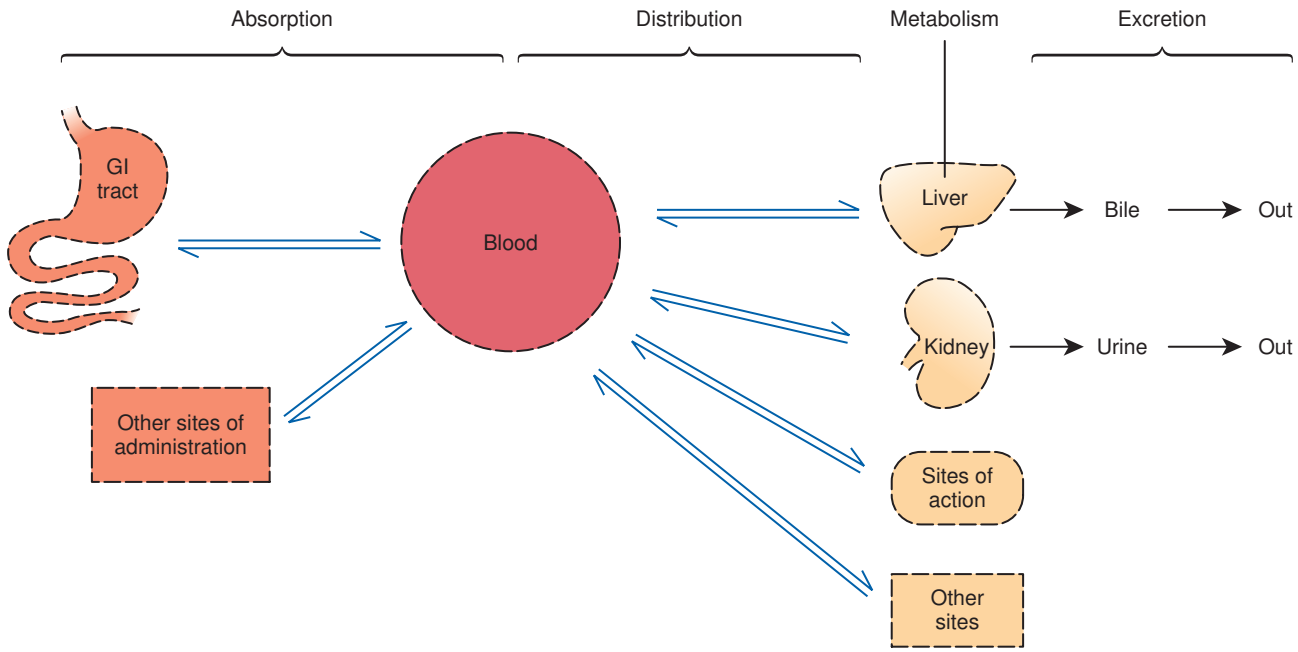

Fig. 4.1 The Four Basic Pharmacokinetic Processes. Dotted lines represent membranes that must be crossed as drugs move throughout the body. *GI*, Gastrointestinal.

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 very 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

Very 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.

Transport systems are an important means of drug transit. For example, certain orally administered drugs could not be absorbed unless there were transport systems to move them across the membranes that separate the lumen of the intestine from the blood. 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 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 very small 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

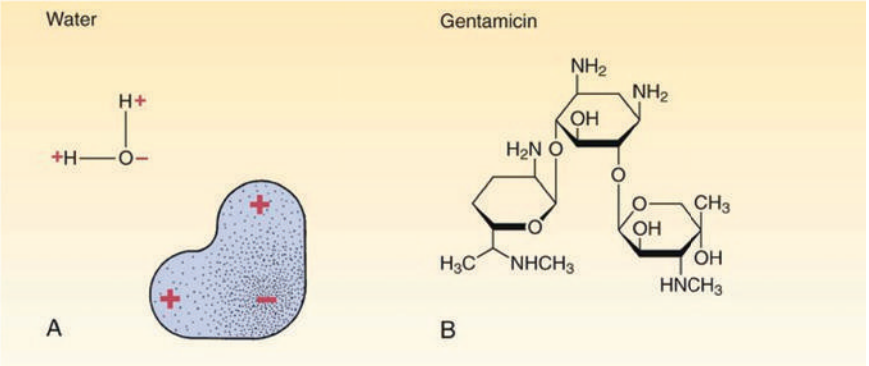

Fig. 4.2 Polar molecules. (A) Stippling shows the distribution of electrons within the water molecule. As indicated at the lower right, water's electrons spend more time near the oxygen atom than near the hydrogen atoms, making the area near the oxygen atom somewhat negative and the area near the hydrogen 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.

such as gastric acid because they remain in a nonionized form. When aspirin molecules pass from the stomach into the 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 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 acidic media, *when there is a pH gradient between two sides of a membrane,* the following occur:

- Acidic drugs accumulate on the alkaline side.
- Basic drugs accumulate on the acidic side.

The process whereby a drug accumulates on the side of a membrane where the pH most favors its ionization is referred to as *pH partitioning or ion trapping.*

ABSORPTION

Absorption is defined as *the movement of a drug from its site of administration into the systemic circulation.* The *rate* of absorption determines how *soon* effects will begin. The *amount* of absorption helps determine how *intense* effects will be. Two other terms associated with absorption are *chemical equivalence* and *bioavailability.* Drug preparations are considered *chemically equivalent* if they contain the same amount of the identical chemical compound (drug). Preparations are considered equal in *bioavailability* if the drug they contain is absorbed at the same rate and to the same extent. It is possible for two formulations of the same drug to be chemically equivalent while differing in bioavailability. The concept of bioavailability is discussed further in Chapter 6.

Factors Affecting Drug Absorption

The rate at which a drug undergoes absorption is influenced by the physical and chemical properties of the drug and by physiologic and anatomic factors at the absorption site.

Rate of Dissolution

Before a drug can be absorbed, it must first dissolve. Hence the rate of dissolution helps determine the rate of absorption. Drugs in formulations that allow rapid dissolution have a faster onset than drugs formulated for slow dissolution.

Surface Area

The surface area available for absorption is a major determinant of the rate of absorption. When the surface area is larger, absorption is faster. For this reason, absorption of orally administered drugs is usually greater from the small intestine rather than from the stomach. (Recall that the small intestine, because of its lining of microvilli, has an extremely large surface area, whereas the surface area of the stomach is relatively small.)

Blood Flow

Drugs are absorbed most rapidly from sites where blood flow is high because blood containing a newly absorbed drug will be replaced rapidly by drug-free blood, thereby maintaining a large gradient between the concentration of drug outside the blood and the concentration of drug in the blood. The greater the concentration gradient, the more rapid absorption will be.

Lipid Solubility

As a rule, highly lipid-soluble drugs are absorbed more rapidly than drugs whose lipid solubility is low. This occurs because lipid-soluble drugs can readily cross the membranes that separate them from the blood, whereas drugs of low lipid solubility cannot.

pH Partitioning

pH partitioning can influence drug absorption. Absorption will be enhanced when the difference between the pH of plasma and the pH at the site of administration is such that drug molecules will have a greater tendency to be ionized in the plasma.

Characteristics of Commonly Used Routes of Administration

For each of the major routes of administration—oral (PO), intravenous (IV), intramuscular (IM), and subcutaneous (subQ)—the pattern of drug absorption (i.e., the rate and extent of absorption) is unique. Consequently, the route by which a drug is administered significantly affects both the onset and the intensity of effects. The distinguishing characteristics of the four major routes are summarized in Table 4.1. Additional routes of administration (e.g., topical, transdermal, inhaled) each have unique characteristics that are addressed throughout the book as we discuss specific drugs that use them.

DISTRIBUTION

Distribution is defined as *the movement of drugs from the systemic circulation to the site of drug action.* Drug distribution is determined by three major factors: blood flow to tissues, the ability of a drug to exit the vascular system, and, to a lesser extent, the ability of a drug to enter cells.

Blood Flow to Tissues

In the first phase of distribution, drugs are carried by the blood to the tissues and organs of the body. The rate at which drugs are delivered to a particular tissue is determined by blood flow to that tissue. Because most tissues are well perfused, regional blood flow is rarely a limiting factor in drug distribution.

There are two pathologic conditions—abscesses and tumors—in which low regional blood flow can affect drug therapy. An abscess has no internal blood vessels; therefore, because abscesses lack a blood supply, antibiotics cannot reach the bacteria within. Accordingly, if drug therapy is to be effective, the abscess must usually be surgically drained.

Solid tumors have a limited blood supply. Although blood flow to the outer regions of tumors is relatively high, blood flow becomes progressively lower toward the core. As a result, it may not be possible to achieve high drug levels deep inside tumors. Limited blood flow is a major reason that solid tumors are resistant to drug therapy.

Exiting the Vascular System

After a drug has been delivered to an organ or tissue by blood circulation, the next step is to exit the vasculature. Because most drugs do not produce their effects within the blood, the ability to leave the vascular system is an important determinant of drug actions. Drugs in the vascular system leave the blood at capillary beds.

Typical Capillary Beds

Most capillary beds offer no resistance to the departure of drugs because, in most tissues, drugs can leave the vasculature simply by passing through pores in the capillary wall. Because drugs pass *between* capillary cells rather

TABLE 4.1 Properties of Major Routes of Drug Administration

Route	Barriers to Absorption	Absorption Pattern	Advantages	Disadvantages
Parenteral				
Intravenous (IV)	None (absorption is bypassed)	Instantaneous	Rapid onset, and hence ideal for emergencies Precise control over drug levels Permits use of large fluid volumes Permits use of irritant drugs	Irreversible Expensive Inconvenient Difficult to do, and hence poorly suited for self-administration Risk for fluid overload, infection, and embolism Drug must be water soluble
Intramuscular (IM)	Capillary wall (easy to pass)	Rapid with water-soluble drugs Slow with poorly soluble drugs	Permits use of poorly soluble drugs Permits use of depot preparations	Possible discomfort Inconvenient Potential for injury
Subcutaneous (subQ)	Same as IM	Same as IM	Same as IM	Same as IM
Enteral				
Oral (PO)	Epithelial lining of gastrointestinal tract; capillary wall	Slow and variable	Easy Convenient Inexpensive Ideal for self-medication Potentially reversible, and hence safer than parenteral routes	Variability Inactivation of some drugs by gastric acid and digestive enzymes Possible nausea and vomiting from local irritation Patient must be conscious and cooperative.

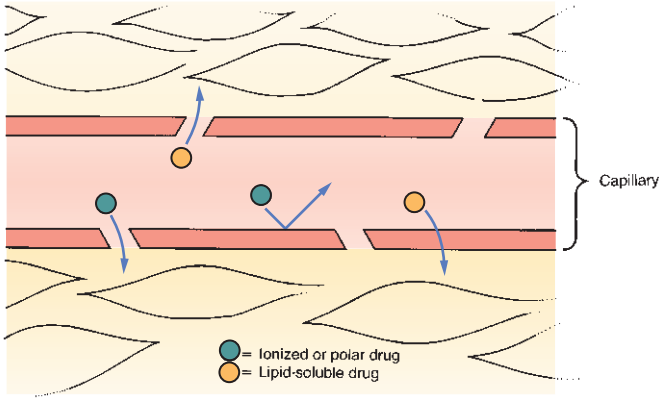

Fig. 4.3 Drug Movement at Typical Capillary Beds. In most capillary beds, "large" gaps exist between the cells that compose the capillary wall. Drugs and other molecules can pass freely into and out of the bloodstream through these gaps. As illustrated, lipid-soluble compounds can also pass directly through the cells of the capillary wall.

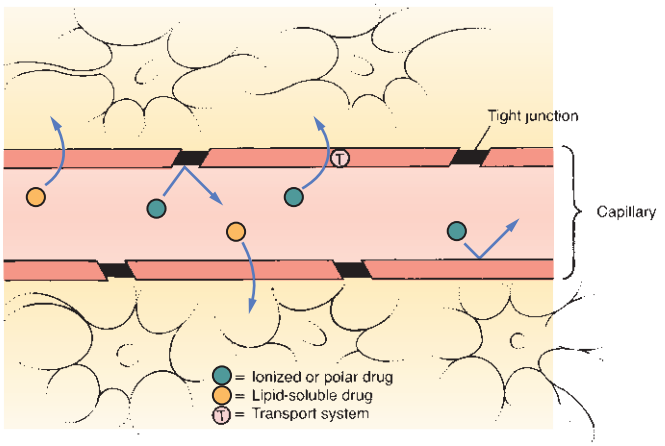

Fig. 4.4 Drug Movement Across the Blood-Brain Barrier. Tight junctions between cells that compose the walls of capillaries in the central nervous system prevent drugs from passing between cells to exit the vascular system. Consequently, to reach sites of action within the brain, a drug must pass directly through cells of the capillary wall. To do this, the drug must be lipid soluble or be able to use an existing transport system.

than *through* them, movement into the interstitial space is not impeded. The exit of drugs from a typical capillary bed is depicted in Fig. 4.3.

Blood–Brain Barrier

The term *blood–brain barrier* (BBB) refers to the unique anatomy of capillaries in the central nervous system (CNS). As shown in Fig. 4.4, there are *tight junctions* between the cells that compose the walls of most capillaries in the CNS. These junctions are so tight that they prevent drug passage. Consequently, to leave the blood and reach sites of action within the brain, a drug must be able to pass *through* cells of the capillary wall. Only drugs that are *lipid soluble* or have a *transport system* can cross the BBB to a significant degree.

Recent evidence indicates that, in addition to tight junctions, the BBB has another protective component: *PGP*. As noted earlier, PGP is a transporter that pumps a variety of drugs out of cells. In capillaries of the CNS, PGP pumps drugs back into the blood and thereby limits their access to the brain.

The BBB is not fully developed at birth. As a result, newborns have heightened sensitivity to medicines that act on the brain. Likewise, neonates are especially vulnerable to CNS toxicity.

Placental Drug Transfer

The membranes of the placenta separate the maternal circulation from the fetal circulation (Fig. 4.5). *However, the membranes of the placenta do NOT constitute an absolute barrier to the passage of drugs.* The same factors that determine the movement of drugs across other membranes determine the movement of drugs across the placenta. Most drugs cross the placenta via simple diffusion. Lipid-soluble, nonionized compounds

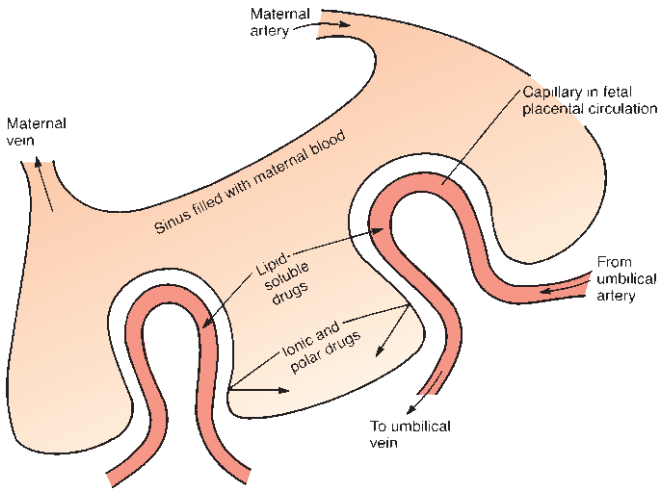

Fig. 4.5 Placental Drug Transfer. To enter the fetal circulation, drugs must cross membranes of the maternal and fetal vascular systems. Lipid-soluble drugs can readily cross these membranes and enter the fetal blood, whereas ions and polar molecules are prevented from reaching the fetal blood.

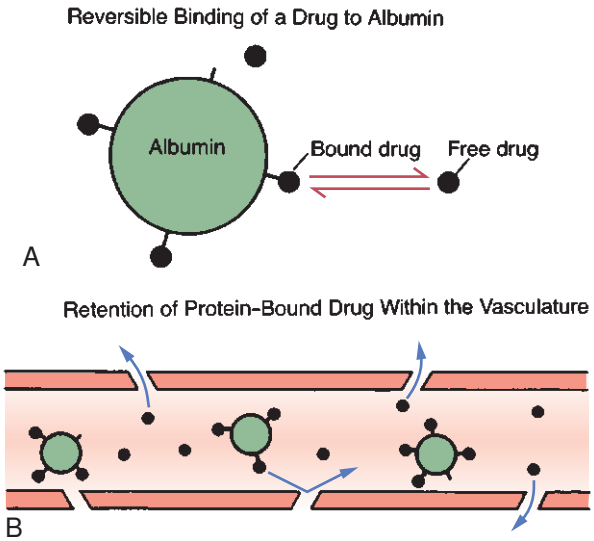

Fig. 4.6 Protein Binding of Drugs. (A) Albumin is the most prevalent protein in plasma and the most important of the proteins to which drugs bind. (B) Only unbound (free) drug molecules can leave the vascular system. Bound molecules are too large to fit through the pores in the capillary wall.

readily pass from the maternal bloodstream into the blood of the fetus. In contrast, compounds that are ionized, highly polar, or protein bound are largely excluded—as are drugs that are substrates for the PGP transporter that can pump a variety of drugs out of placental cells into the maternal blood.

Protein Binding

Drugs can form reversible bonds with various proteins in the body. Of all the proteins with which drugs can bind, *plasma albumin* is the most important. Like other proteins, albumin is a large molecule. Because of its size, albumin is too large to leave the bloodstream.

Fig. 4.6 depicts the binding of drug molecules to albumin. Note that the drug molecules are much smaller than albumin. As indicated by the two-way arrows, binding between albumin and drugs is *reversible.* Hence drugs may be *bound* or *unbound* (free).

Even though a drug can bind albumin, only some molecules will be bound at any moment. The percentage of drug molecules that are bound is determined by the strength of the attraction between albumin and the drug. For example, the attraction between albumin and the anticoagulant warfarin is strong, causing nearly all (99%) of the warfarin molecules in plasma to be bound, leaving only 1% free. On the other hand, the attraction between the antibiotic gentamicin and albumin is relatively weak; less than 10% of the gentamicin molecules in plasma are bound, leaving more than 90% free.

An important consequence of protein binding is restriction of drug distribution. Because albumin is too large to leave the bloodstream, drug molecules that are bound to albumin cannot leave either (see Fig. 4.6B). As a result, bound molecules cannot reach their sites of action or undergo metabolism or excretion until the drug–protein bond is broken so that the drug is free to leave the circulation.

In addition to restricting drug distribution, protein binding can be a source of drug interactions. As suggested by Fig. 4.6A, each molecule of albumin has only a few sites to which drug molecules can bind. Because the number of binding sites is limited, drugs with the ability to bind albumin will compete with one another for those sites. As a result, one drug can displace another from albumin, causing the free concentration of the displaced drug to rise, thus increasing the intensity of drug responses. If plasma drug levels rise sufficiently, toxicity can result.

Entering Cells

Many drugs produce their effects by binding with receptors located on the external surface of the cell membrane; however, some drugs must enter cells to reach their sites of action, and practically all drugs must enter cells to undergo metabolism and excretion. The factors that determine the ability of a drug to cross cell membranes are the same factors that determine the passage of drugs across all other membranes, namely lipid solubility, the presence of a transport system, or both.

METABOLISM

Drug metabolism, also known as *biotransformation,* is defined as *the enzymatic alteration of drug structure.* Most drug metabolism takes place in the liver.

Hepatic Drug-Metabolizing Enzymes

Most drug metabolism that takes place in the liver is performed by the *hepatic microsomal enzyme system,* also known as the *P450 system.* The term *P450* refers to *cytochrome P450,* a key component of this enzyme system.

It is important to appreciate that cytochrome P450 is not a single molecular entity but rather a group of 12 closely related enzyme families. Three of the cytochrome P450 (CYP) families—designated CYP1, CYP2, and CYP3—metabolize drugs. The other nine families metabolize endogenous compounds (e.g., steroids, fatty acids). Each of the three P450 families that metabolize drugs is composed of multiple forms, each of which metabolizes only certain drugs. To identify the individual forms of cytochrome P450, designations such as CYP1A2, CYP2D6, and CYP3A4 are used to indicate specific members of the CYP1, CYP2, and CYP3 families, respectively.

Therapeutic Consequences of Drug Metabolism

Drug metabolism has six possible consequences of therapeutic significance:

- Accelerated renal excretion of drugs
- Drug inactivation

- Increased therapeutic action
- Activation of prodrugs
- Increased toxicity
- Decreased toxicity

Accelerated Renal Drug Excretion

The most important consequence of drug metabolism is promotion of renal drug excretion. The kidneys, which are the major organs of drug excretion, are unable to excrete drugs that are highly lipid soluble. Hence, by converting lipid-soluble drugs into more hydrophilic (water-soluble) forms, metabolic conversion can accelerate renal excretion of many agents.

Drug Inactivation

Drug metabolism can convert pharmacologically active compounds to inactive forms. This is the most common end result of drug metabolism.

Increased Therapeutic Action

Metabolism can increase the effectiveness of some drugs. For example, metabolism converts codeine into morphine. The analgesic activity of morphine is so much greater than that of codeine that formation of morphine may account for virtually all the pain relief that occurs after codeine administration.

Activation of Prodrugs

A *prodrug* is a compound that is pharmacologically inactive as administered and then undergoes conversion to its active form through metabolism. Prodrugs have several advantages; for example, a drug that cannot cross the BBB may be able to do so as a lipid-soluble prodrug that is converted to the active form in the CNS.

Increased or Decreased Toxicity

By converting drugs into inactive forms, metabolism can decrease toxicity. Conversely, metabolism can increase the potential for harm by converting relatively safe compounds into forms that are toxic. Increased toxicity is illustrated by the conversion of acetaminophen into a hepatotoxic metabolite. It is this product of metabolism, and not acetaminophen itself, that causes injury when acetaminophen is taken in overdose.

Special Considerations in Drug Metabolism

Several factors can influence the rate at which drugs are metabolized. These must be accounted for in drug therapy.

Age

The drug-metabolizing capacity of infants is limited. The liver does not develop its full capacity to metabolize drugs until approximately 1 year after birth. During the time before hepatic maturation, infants are especially sensitive to drugs, and care must be taken to avoid injury. Similarly, the ability of older adults to metabolize drugs is commonly decreased. Drug dosages may need to be reduced to prevent drug toxicity.

Induction and Inhibition of Drug-Metabolizing Enzymes

Drugs may be P450 substrates, P450 enzyme inducers, and P450 enzyme inhibitors. Drugs that are metabolized by P450 hepatic enzymes are substrates. Drugs that increase the rate of drug metabolism are inducers. Drugs that decrease the rate of drug metabolism are called *inhibitors.* Often a drug may have more than one property. For example, a drug may be both a substrate and an inducer.

Inducers act on the liver to stimulate enzyme synthesis. This process is known as *induction.* By increasing the rate of drug metabolism, the amount of active drug is decreased and plasma drug levels fall. If dosage adjustments are not made to accommodate for this, a drug may not achieve therapeutic levels.

Inhibitors act on the liver through a process known as *inhibition.* By slowing the rate of metabolism, inhibition can cause an increase in active drug accumulation. This can lead to an increase in adverse effects and toxicity.

First-Pass Effect

The term *first-pass effect* refers to the rapid hepatic inactivation of certain oral drugs. When drugs are absorbed from the gastrointestinal tract, they are carried directly to the liver through the hepatic portal vein before they enter the systemic circulation. If the capacity of the liver to metabolize a drug is extremely high, that drug can be completely inactivated on its first pass through the liver. As a result, no therapeutic effects can occur. To circumvent the first-pass effect, a drug that undergoes rapid hepatic metabolism is often administered parenterally. This permits the drug to temporarily bypass the liver, thereby allowing it to reach therapeutic levels in the systemic circulation before being metabolized.

Nutritional Status

Hepatic drug-metabolizing enzymes require a number of cofactors to function. In the malnourished patient, these cofactors may be deficient, causing drug metabolism to be compromised.

Competition Between Drugs

When two drugs are metabolized by the same metabolic pathway, they may compete with each other for metabolism and may thereby decrease the rate at which one or both agents are metabolized. If metabolism is depressed enough, a drug can accumulate to dangerous levels.

Enterohepatic Recirculation

As noted earlier and depicted in Fig. 4.7, enterohepatic recirculation is a repeating cycle in which a drug is transported from the liver into the duodenum (through the bile duct) and then back to the liver (through the portal blood). However, it is important to note that only certain drugs are affected. Specifically, the process is limited to drugs that have undergone *glucuronidation,* a process that converts lipid-soluble drugs to water-soluble drugs by binding them to glucuronic acid. After glucuronidation, these drugs can enter the bile and then pass to the duodenum. In the intestine, some drugs can be hydrolyzed by intestinal β-glucuronidase, an enzyme that breaks the bond between the original drug and the glucuronide moiety, thereby releasing the free drug. Because the free drug is more lipid soluble than the glucuronidated form, the free drug can undergo reabsorption across the intestinal wall, followed by transport back to the liver, where the cycle can start again. Because of enterohepatic recycling, drugs can remain in the body much longer than they otherwise would.

EXCRETION

Drug excretion is defined as *the removal of drugs from the body.* Drugs and their metabolites can exit the body in urine, bile, sweat, saliva, breast milk, and expired air. The most important organ for drug excretion is the kidney.

Renal Drug Excretion

The kidneys account for the majority of drug excretion. When the kidneys are healthy, they serve to limit the duration of action of many drugs. Conversely, if renal failure occurs, both the duration and intensity of drug responses may increase.

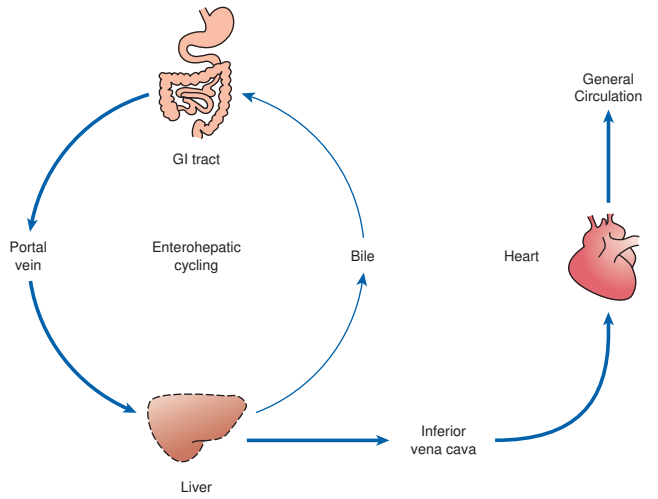

Fig. 4.7 Movement of Drugs After Gastrointestinal *(GI)* Absorption. All drugs absorbed from sites along the GI tract—stomach, small intestine, and large intestine (but not the oral mucosa or distal rectum)—must go through the liver, through the portal vein, on their way to the heart and then the general circulation. For some drugs, passage is uneventful. Others undergo extensive hepatic metabolism, and still others undergo *enterohepatic recirculation,* a repeating cycle in which a drug moves from the liver into the duodenum (through the bile duct) and then back to the liver (through the portal blood). As discussed in the text under *Enterohepatic Recirculation,* the process is limited to drugs that have first undergone hepatic glucuronidation.

Steps in Renal Drug Excretion

Urinary excretion is the net result of three processes: (1) glomerular filtration, (2) passive tubular reabsorption, and (3) active tubular secretion.

Glomerular filtration. Renal excretion begins at the glomerulus of the kidney tubule. As blood flows through the glomerular capillaries, fluids and small molecules—including drugs—are forced through the pores of the capillary wall. This process, called *glomerular filtration,* moves drugs from the blood into the tubular urine. Blood cells and large molecules (e.g., proteins) are too big to pass through the capillary pores and therefore do not undergo filtration. Because large molecules are not filtered, drugs bound to albumin remain in the blood.

Passive tubular reabsorption. As depicted in Fig. 4.8, the vessels that deliver blood to the glomerulus return to proximity with the renal tubule at a point distal to the glomerulus. At this distal site, drug concentrations in the blood are lower than drug concentrations in the tubule. This concentration gradient acts as a driving force to move drugs from the lumen of the tubule back into the blood. Because lipid-soluble drugs can readily cross the membranes that compose the tubular and vascular walls, *drugs that are lipid soluble undergo passive reabsorption from the tubule back into the blood.* In contrast, drugs that are not lipid soluble (ions and polar compounds) remain in the urine to be excreted.

Active tubular secretion. There are active transport systems in the kidney tubules that pump drugs from the blood to the tubular urine. These pumps have a relatively high capacity and play a significant role in excreting certain compounds.

Factors That Modify Renal Drug Excretion

Renal drug excretion varies from patient to patient. Conditions such as chronic renal disease may cause profound alterations. Three other important factors to consider are pH-dependent ionization, competition for active tubular transport, and patient age.

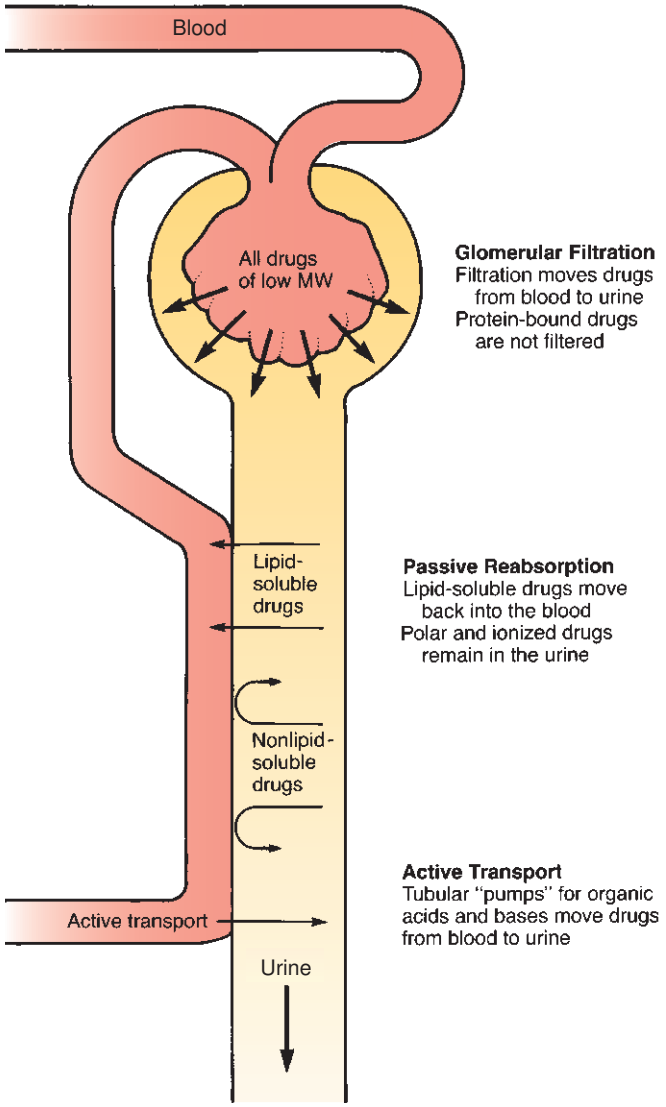

Fig. 4.8 Renal Drug Excretion. *MW,* Molecular weight.

pH-dependent ionization. The phenomenon of pH-dependent ionization can be used to accelerate renal excretion of drugs. Recall that passive tubular reabsorption is limited to lipid-soluble compounds. Because ions are not lipid soluble, drugs that are ionized at the pH of tubular urine will remain in the tubule and be excreted. Consequently, by manipulating urinary pH in such a way as to promote the ionization of a drug, we can decrease passive reabsorption back into the blood and can thereby hasten the drug's elimination. This principle has been used to promote the excretion of poisons and medications that have been taken in toxic doses.

Competition for active tubular transport. Competition between drugs for active tubular transport can delay renal excretion, thereby prolonging effects. The active transport systems of the renal tubules can be envisioned as motor-driven revolving doors that carry drugs from the plasma into the renal tubules. These "revolving doors" can carry only a limited number of drug molecules per unit of time. Accordingly, if there are too many molecules present, some must wait their turn. Because of competition, if we administer two drugs at the same time and if both drugs use the same transport system, excretion of each will be delayed by the presence of the other.

Age. The kidneys of newborns are not fully developed. Until their kidneys reach full capacity (a few months after birth), infants have a limited capacity to excrete drugs. This must be accounted for when medicating an infant.

In older adults, renal function often declines. Older adults have smaller kidneys and fewer nephrons. The loss of nephrons results in decreased blood filtration. In addition, vessel changes such as atherosclerosis reduce renal blood flow. As a result, renal excretion of drugs is decreased.

Nonrenal Routes of Drug Excretion

In most cases, excretion of drugs by nonrenal routes has minimal clinical significance. However, in certain situations, nonrenal excretion can have important therapeutic and toxicologic consequences.

Breast Milk

Some drugs taken by breast-feeding women can undergo excretion into milk. As a result, breastfeeding can expose the nursing infant to drugs. The factors that influence the appearance of drugs in breast milk are the same factors that determine the passage of drugs across membranes. Accordingly, lipid-soluble drugs have ready access to breast milk, whereas drugs that are polar, ionized, or protein bound cannot enter in significant amounts.

Other Nonrenal Routes of Excretion

The *bile* is an important route of excretion for certain drugs. Because bile is secreted into the small intestine, drugs that do not undergo enterohepatic recirculation leave the body in the feces.

The *lungs* are the major route by which volatile anesthetics are excreted. Alcohol is partially eliminated by this route.

Small amounts of drugs can appear in *sweat* and *saliva.* These routes have little therapeutic or toxicologic significance.

TIME COURSE OF DRUG RESPONSES

It is possible to regulate the time at which drug responses start, the time they are most intense, and the time they cease. Because the four pharmacokinetic processes—absorption, distribution, metabolism, and excretion—determine how much drug will be at its sites of action at any given time, these processes are the major determinants of the time course over which drug responses take place.

Plasma Drug Levels

In most cases the time course of drug action bears a direct relationship to the concentration of a drug in the blood. Hence, before discussing the time course per se, we need to review several important concepts related to plasma drug levels.

Clinical Significance of Plasma Drug Levels

Providers frequently monitor plasma drug levels in efforts to regulate drug responses. When measurements indicate that drug levels are inappropriate, these levels can be adjusted up or down by changing dosage size, dosage timing, or both.

The practice of regulating plasma drug levels to control drug responses should seem a bit odd, given that (1) drug responses are related to drug concentrations at sites of action and (2) the site of action of most drugs is not in the blood. More often than not, it is a practical impossibility to measure drug concentrations at sites of action. Experience has shown that, for most drugs, *there is a direct correlation between therapeutic and toxic responses and the amount of drug present in plasma.* Therefore, although we cannot usually measure drug concentrations at sites of action, we *can* determine plasma drug concentrations that, in turn, are highly predictive of therapeutic and toxic responses. Accordingly, the dosing objective is commonly spoken of in terms of achieving a specific plasma level of a drug.

Two Plasma Drug Levels Defined

Two plasma drug levels are of special importance: (1) the minimum effective concentration (MEC) and (2) the toxic concentration. These levels are depicted in Fig. 4.9.

Minimum effective concentration. The MEC is defined as *the plasma drug level less than which therapeutic effects will not occur.* Hence, to be of benefit, a drug must be present in concentrations at or greater than the MEC.

Toxic concentration. Toxicity occurs when plasma drug levels climb too high. The plasma level at which toxic effects begin is termed the *toxic concentration.* Doses must be kept small enough so that the toxic concentration is not reached.

Therapeutic Range

As indicated in Fig. 4.9, there is a range of plasma drug levels, falling between the MEC and the toxic concentration, which is termed the *therapeutic range.* When plasma levels are within the therapeutic range, there is enough drug present to produce therapeutic responses but not so much that toxicity results. *The objective of drug dosing is to maintain plasma drug levels within the therapeutic range.*

The width of the therapeutic range is a major determinant of the ease with which a drug can be used safely. Drugs that have a narrow therapeutic range are difficult to administer safely. Conversely, drugs that have a wide therapeutic range can be administered safely with relative ease. The principle is the same as that of the therapeutic index discussed in Chapter 3. The therapeutic range is quantified, or measured, by the therapeutic index.

Understanding the concept of therapeutic range can facilitate patient care. Because drugs with a narrow therapeutic range are more dangerous than drugs with a wide therapeutic range, patients taking drugs with a narrow therapeutic range are the most likely to require intervention for drug-related complications. The provider who is aware of this fact can focus additional attention on monitoring these patients for signs and symptoms of toxicity.

Single-Dose Time Course

Fig. 4.9 shows how plasma drug levels change over time after a single dose of an oral medication. Drug levels rise as the medicine undergoes

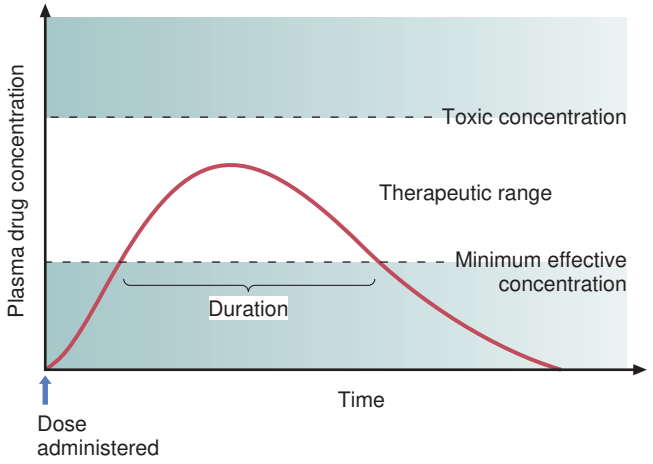

Fig. 4.9 Single-Dose Time Course.

absorption. Drug levels then decline as metabolism and excretion eliminate the drug from the body.

Because responses cannot occur until plasma drug levels have reached the MEC, there is a latent period between drug administration and onset of effects. The extent of this delay is determined by the rate of absorption.

The duration of effects is determined largely by the combination of metabolism and excretion. As long as drug levels remain greater than the MEC, therapeutic responses will be maintained; when levels fall to less than the MEC, benefits will cease. Because metabolism and excretion are the processes most responsible for causing plasma drug levels to fall, these processes are the primary determinants of how long drug effects will persist.

Drug Half-Life

Before proceeding to the topic of multiple dosing, we need to discuss the concept of half-life. When a patient ceases drug use, the combination of metabolism and excretion will cause the amount of drug in the body to decline. The half-life of a drug is an index of just how rapidly that decline occurs for most drugs. The concept of half-life does not apply to the elimination of all drugs. A few agents, most notably ethanol (alcohol), leave the body at a *constant rate,* regardless of how much is present. The implications of this kind of decline for ethanol are discussed in Chapter 32.

Drug half-life is defined as *the time required for the amount of drug in the body to decrease by 50%.* A few drugs have half-lives that are extremely short—on the order of minutes or less. In contrast, the half-lives of some drugs exceed 1 week.

Note that, in our definition of half-life, a *percentage*—not a specific *amount*—of drug is lost during one half-life. That is, the half-life does not specify, for example, that 2 g or 18 mg will leave the body in a given time. Rather, the half-life tells us that, no matter what the amount of drug in the body may be, half (50%) will leave during a specified period of time (the half-life). The actual amount of drug that is lost during one half-life depends on just how much drug is present: the more drug in the body, the larger the amount lost during one half-life.

The concept of half-life is best understood through an example. Morphine provides a good illustration. The half-life of morphine is approximately 3 hours. By definition, this means that body stores of morphine will decrease by 50% every 3 hours—regardless of how much morphine is in the body. If there are 50 mg of morphine in the body, 25 mg (50% of 50 mg) will be lost in 3 hours; if there are only 2 mg of morphine in the body, only 1 mg (50% of 2 mg) will be lost in 3 hours. Note that, in both cases, morphine levels drop by 50% during an interval of one half-life. However, the actual *amount* lost is larger when total body stores of the drug are higher.

The half-life of a drug determines the dosing interval (i.e., how much time separates each dose). For drugs with a short half-life, the dosing interval must be correspondingly short. If a long dosing interval is used, drug levels will fall to less than the MEC between doses, and therapeutic effects will be lost. Conversely, if a drug has a long half-life, a long time can separate doses without loss of benefits.

Drug Levels Produced With Repeated Doses

Multiple dosing leads to drug accumulation. When a patient takes a single dose of a drug, plasma levels simply go up and then come back down. In contrast, when a patient takes repeated doses of a drug, the process is more complex and results in drug accumulation. The factors that determine the rate and extent of accumulation are considered next.

Plateau Drug Levels

Administering repeated doses will cause a drug to build up in the body until a *plateau* (steady level) has been achieved. What causes drug levels to reach plateau? If a second dose of a drug is administered before all of the prior dose has been eliminated, total body stores of that drug will be higher after the second dose than after the initial dose. As succeeding doses are administered, drug levels will climb even higher. The drug will continue to accumulate until a state has been achieved in which the amount of drug eliminated between doses equals the amount administered. *When the amount of drug eliminated between doses equals the dose administered, average drug levels will remain constant and plateau will have been reached* (Fig. 4.10).

Time to Plateau

When a drug is administered repeatedly in the same dose, *plateau will be reached in approximately four half-lives.* For the hypothetical agent illustrated in Fig. 4.10, total body stores approached their peak near the beginning of day 5, or approximately 4 full days after treatment began. Because the half-life of this drug is 1 day, reaching plateau in 4 days is equivalent to reaching plateau in four half-lives.

As long as dosage remains constant, the time required to reach plateau is independent of dosage size. Put another way, the time required to reach plateau when giving repeated large doses of a particular drug is identical to the time required to reach plateau when giving repeated small doses of that drug. Referring to the drug in Fig. 4.10, just as it took four half-lives (4 days) to reach plateau when a dose of 2 g was administered daily, it would also take four half-lives to reach plateau if a dose of 4 g were administered daily. It is true that the *height* of the plateau would be greater if a 4-g dose were given, but the time required to reach plateau would not be altered by the increase in dosage. To confirm this statement, substitute a dose of 4 g in the previous exercise and see when plateau is reached.

Techniques for Reducing Fluctuations in Drug Levels

As illustrated in Fig. 4.10, when a drug is administered repeatedly, its level will fluctuate between doses. The highest level is referred to as the *peak concentration,* and the lowest level is referred to as the *trough concentration.* The acceptable height of the peaks and troughs will depend on the drug's therapeutic range: the peaks must be kept less than the toxic concentration, and the troughs must be kept greater than the MEC. If there is not much difference between the toxic concentration and the MEC, then fluctuations must be kept to a minimum.

Three techniques can be used to reduce fluctuations in drug levels. One technique is to *administer drugs by continuous infusion.* With this

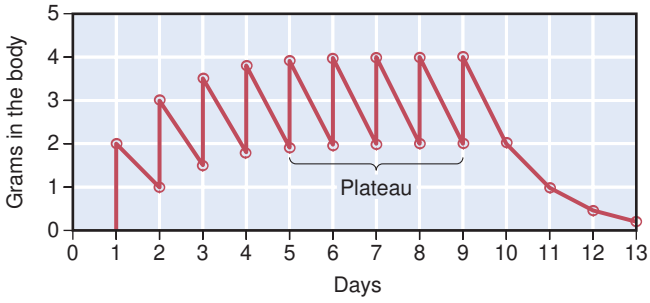

Fig. 4.10 Drug Accumulation With Repeated Administration. The drug has a half-life of 1 day. The dosing schedule is 2 g given once a day on days 1 through 9. Note that plateau is reached at about the beginning of day 5 (i.e., after four half-lives). Note also that, when administration is discontinued, it takes approximately 4 days (four half-lives) for most (94%) of the drug to leave the body.

procedure, plasma levels can be kept nearly constant. Another is to *administer a depot preparation,* which releases the drug slowly and steadily. The third is to *reduce both the size of each dose and the dosing interval* (keeping the total daily dose constant). For example, rather than giving the drug from Fig. 4.10 in 2-g doses once every 24 hours, we could give this drug in 1-g doses every 12 hours. With this altered dosing schedule, the total daily dose would remain unchanged, as would total body stores at plateau. However, instead of fluctuating over a range of 2 g between doses, levels would fluctuate over a range of 1 g.

Loading Doses Versus Maintenance Doses

As discussed previously, if we administer a drug in repeated doses of *equal size,* an interval equivalent to approximately four half-lives is required to achieve plateau. When plateau must be achieved more quickly, a large initial dose can be administered. This large initial dose is called a *loading dose.* After high drug levels have been established with a loading dose, plateau can be maintained by giving smaller doses. These smaller doses are referred to as *maintenance doses.*

The claim that use of a loading dose will shorten the time to plateau may appear to contradict an earlier statement, which said that the time to plateau is not affected by dosage size. However, there is no contradiction. For any *specified dosage,* it will always take about four half-lives to reach plateau. When a loading dose is administered followed by maintenance doses, the plateau is not reached *for the loading dose.* Rather, we have simply used the loading dose to rapidly produce a drug level equivalent to the plateau level for a smaller dose. To achieve plateau level for the loading dose, it would be necessary to either administer repeated doses equivalent to the loading dose for a period of four half-lives or administer a dose even larger than the original loading dose.

Decline From Plateau

When drug administration is discontinued, most (94%) of the drug in the body will be eliminated over an interval equal to approximately four half-lives. The time required for drugs to leave the body is important when toxicity develops. If a drug has a short half-life, body stores will decline rapidly, thereby making management of overdose less difficult. However, when an overdose of a drug with a long half-life occurs, toxic levels of the drug will remain in the body for a long time. Additional management may be needed in these instances.

PHARMACODYNAMICS

Pharmacodynamics is the study of the biochemical and physiologic effects of drugs on the body and the molecular mechanisms by which those effects are produced. To participate rationally in achieving the therapeutic objective, an understanding of pharmacodynamics is essential.

DOSE–RESPONSE RELATIONSHIPS

The dose–response relationship (i.e., the relationship between the size of an administered dose and the intensity of the response produced) is a fundamental concern in therapeutics. Dose–response relationships determine the minimal amount of drug needed to elicit a response, the maximal response a drug can elicit, and how much to increase the dosage to produce the desired increase in response.

Basic Features of the Dose–Response Relationship

The basic characteristics of dose–response relationships are illustrated in Fig. 4.11. Part A shows dose–response data plotted on *linear* coordinates. Part B shows the same data plotted on *semilogarithmic* coordinates (i.e., the scale on which dosage is plotted is logarithmic rather than linear). The most obvious and important characteristic revealed by these curves is that the dose–response relationship is *graded.* That is, as the dosage increases, the response becomes progressively larger. Because drug responses are graded, therapeutic effects can be adjusted to fit the needs of each patient by raising or lowering the dosage until a response of the desired intensity is achieved.

As indicated in Fig. 4.11, the dose–response relationship can be viewed as having three phases. Phase 1 (see Fig. 4.11B) occurs at low

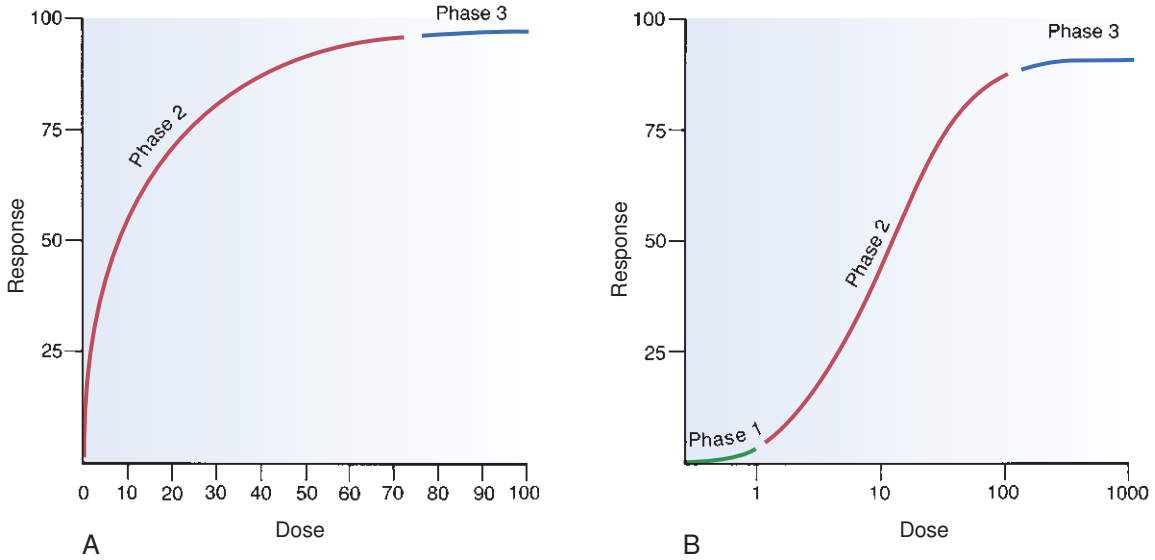

Fig. 4.11 Basic Components of the Dose-Response Curve. (A) A dose–response curve with dose plotted on a linear scale. (B) The same dose–response relationship shown in A but with the dose plotted on a logarithmic scale. Note the three phases of the dose–response curve: *Phase 1,* The curve is relatively flat; doses are too low to elicit a significant response. *Phase 2,* The curve climbs upward as bigger doses elicit correspondingly bigger responses. *Phase 3,* The curve levels off; bigger doses are unable to elicit a further increase in response. (Phase 1 is not indicated in A because very low doses cannot be shown on a linear scale.)

doses. The curve is flat during this phase because doses are too low to elicit a measurable response. During phase 2, an increase in dose elicits a corresponding increase in the response. This is the phase during which the dose–response relationship is graded. As the dose goes higher, eventually a point is reached where an increase in dose is unable to elicit a further increase in response. At this point, the curve flattens out into phase 3.

Maximal Efficacy and Relative Potency

Dose–response curves reveal two characteristic properties of drugs: *maximal efficacy* and *relative potency.* Curves that reflect these properties are shown in Fig. 4.12.

Maximal Efficacy

Maximal efficacy is defined as *the largest effect that a drug can produce.* Maximal efficacy is indicated by the *height* of the dose–response curve.

The concept of maximal efficacy is illustrated by the dose–response curves for meperidine (Demerol) and pentazocine (Talwin), two morphine-like pain relievers (see Fig. 4.12A). As you can see, the curve for pentazocine levels off at a maximal height less than that of the curve for meperidine. This tells us that the maximal degree of pain relief we can achieve with pentazocine is smaller than the maximal degree of pain relief we can achieve with meperidine. Put another way, no matter how much pentazocine we administer, we can never produce the degree of pain relief that we can with meperidine. Accordingly, we would say that meperidine has greater maximal efficacy than pentazocine.

Despite what intuition might tell us, a drug with very high maximal efficacy is not always more desirable than a drug with lower efficacy. Recall that we want to match the intensity of the response to the patient's needs. This may be difficult to do with a drug that produces extremely intense responses. For example, certain diuretics (e.g., furosemide) have such high maximal efficacy that they can cause dehydration. If we want to mobilize only a modest volume of water, a diuretic with lower maximal efficacy (e.g., hydrochlorothiazide) would be preferred. Similarly, in a patient with a mild headache, we would not select a powerful analgesic (e.g., morphine) for relief. Rather, we would select an analgesic with lower maximal efficacy, such as aspirin.

Relative Potency

The term *potency* refers to the amount of drug we must give to elicit an effect. Potency is indicated by the relative position of the dose-response curve along the *x* (dose) axis.

The concept of potency is illustrated by the curves in Fig. 4.12B. These curves plot doses for two analgesics—morphine and meperidine—versus the degree of pain relief achieved. As you can see, for any particular degree of pain relief, the required dose of meperidine is larger than the required dose of morphine. Because morphine produces pain relief at lower doses than meperidine, we would say that morphine is more potent than meperidine. That is, a potent drug is one that produces its effects at low doses.

Potency is rarely an important characteristic of a drug. The only consequence of having greater potency is that a drug with greater potency can be given in smaller doses.

It is important to note that the potency of a drug implies nothing about its maximal efficacy! Potency and efficacy are completely independent qualities. Drug A can be more effective than drug B even though drug B may be more potent. In addition, drugs A and B can be equally effective even though one may be more potent. As shown in Fig. 4.12B, although meperidine happens to be less potent than morphine, the maximal degree of pain relief that we can achieve with these drugs is identical.

A final comment on the word *potency* is in order. In everyday parlance, people tend to use the word *potent* to express the pharmacologic concept of effectiveness. That is, when most people say, "This drug is very potent," what they mean is, "This drug produces powerful effects." They do not mean, "This drug produces its effects at low doses." In pharmacology, we use the words *potent* and *potency* with the specific and appropriate terminology.

DRUG–RECEPTOR INTERACTIONS

Introduction to Drug Receptors

Drugs produce their effects by interacting with other chemicals. Receptors are the special chemical sites in the body that most drugs interact with to produce effects.

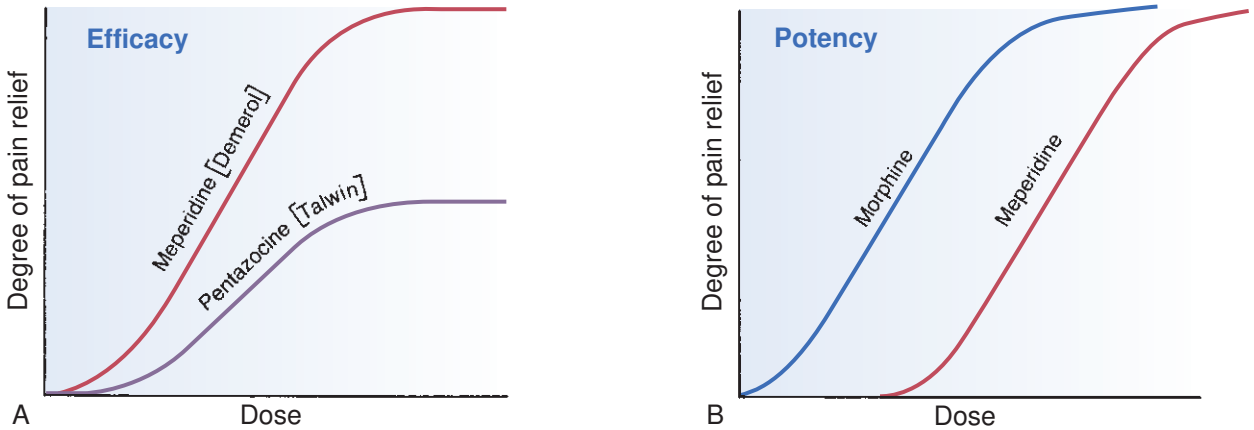

Fig. 4.12 Dose–Response Curves Demonstrating Efficacy and Potency. (A) Efficacy, or maximal efficacy, is an index of the maximal response a drug can produce. The efficacy of a drug is indicated by the height of its dose–response curve. In this example, meperidine has greater efficacy than pentazocine. Efficacy is an important quality in a drug. (B) Potency is an index of how much drug must be administered to elicit a desired response. In this example, achieving pain relief with meperidine requires higher doses than with morphine. We would say that morphine is more potent than meperidine. Note that, if administered in sufficiently high doses, meperidine can produce just as much pain relief as morphine. Potency is usually not an important quality in a drug.