SECOND EDITION

PHARMACOLOGY

FOR THE

PHYSICAL THERAPIST

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Pharmacology for the Physical Therapist

Second Edition

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Contents

Preface

According to the Patient-Centered Primary Care Collaborative, medications are involved in approximately 80% of all treatments and impact *every* aspect of a patient's life. Understanding how the effects of drugs may influence the outcome measures and interventions provided by physical therapists provided the impetus for the first edition of this textbook more than 10 years ago. For example, therapists perform comprehensive assessments of the visual, vestibular, and proprioceptive inputs that control balance to predict an individual's risk of falling. However, this prediction will fall short if the therapist fails to inquire what medications the patient is taking, as many medications—both prescription and over-the-counter—negatively affect balance.

The goal of this book is to provide a comprehensive—yet *focused*—foundation in pharmacology to help rehabilitation professionals understand how medication use may alter the clinical presentation of our patients as well as their responses to therapeutic interventions. In this second edition, two licensed physical therapists (Drs. Jobst and Panus) with extensive training in pharmacology worked closely with Dr. Marieke Kruidering-Hall, a pharmacologist previously involved in medical pharmacology texts.

The information follows the sequence of traditional pharmacology textbooks and integrated organ systems-based curricula. The initial section is a synopsis of the nature of drugs, basic principles of pharmacodynamics and pharmacokinetics, and an overview of the drug development and approval process in the United States. Subsequent chapters include drugs that affect the autonomic and central nervous systems; cardiovascular and pulmonary systems; and the endocrine, gastrointestinal, and musculoskeletal systems. A chemotherapeutic section includes chapters covering anti-microbial drugs, cancer chemotherapy agents, and drugs that modify the immune system.

Each chapter follows a similar outline. A *Case Study* that illustrates how the patient's medications can affect the physical therapy encounter opens the chapter, while the explanation of how the therapy might need to be adjusted closes the chapter. An introductory *Rehabilitation Focus* section highlights the importance of the drugs in the rehabilitation setting. Next, a brief synopsis of relevant pathophysiology is followed by a discussion on the drug classes. Within each drug class, common prototypes, important chemistry, relevant pharmacokinetics, and mechanism(s) of action, as well as physiologic effects, clinical uses, and potential adverse effects are presented. At the end of each chapter, the *Rehabilitation Relevance* section provides a quickly accessible bullet-pointed summary of the adverse drug reactions for the therapist working with patients using these drug classes. End-of-chapter *Questions* are provided to quiz the reader's recall and comprehension.

An accurate medical history is required to provide a correct clinical diagnosis and effective treatment regimen. An essential component of the medical history is the patient's current medication list. The drugs an individual takes have the potential to significantly influence *both* medical and functional outcomes. Rehabilitation therapists often have the privilege of spending more time with patients than other healthcare providers. This privilege comes with the responsibility of understanding patients' responses to medications, recognizing the potential for interactions between responses to medications and therapy interventions, and communicating with key members of the healthcare team and/or the patient when questions or concerns arise regarding potential adverse drug reactions and medication nonadherence. We hope this textbook will assist all healthcare professionals—especially those in physical therapy—in that process.

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Acknowledgments

First, I acknowledge my sincere gratitude to Peter C. Panus. Had I not answered a specific phone call more than ten years ago, I would not have had the opportunity to co-author this textbook and work with such talented colleagues. Second, I would like to thank each of the hundreds of physical therapy students who have taught me how to be a better teacher—both in the classroom and hopefully, on the written page. A very special note of appreciation is due to Dr. Bert Katzung, whose early interest in helping me become a better writer has made a lasting impression. Finally, I would like to thank my husband, Kenneth Tovar, for his consistent encouragement. Nothing productive could have occurred without his patient love and support. To all the individuals that I have undoubtedly forgotten to mention, I express my sincere appreciation.

—Erin E. Jobst

I would first like to express my appreciation to McGraw-Hill for continuing to support the publication of the first and second editions of this textbook. Along with the other authors of this book, I too would like to thank Dr. Bert Katzung, who took a chance that an unknown in both pharmacology education and physical therapy would be able to develop a textbook for physical therapy education. Although not listed as authors in this edition, the input and style of both Dr. Susan B. Masters and Dr. Anthony J. Trevor are also apparent in this edition as well as the first. Finally, I would like to thank my wife, Dr. Leslie W. Panus, who supported me during the writing of this edition and helped proof the final version of these chapters.

—Peter C. Panus

I would like to express my gratitude to Dr. Erin Jobst and Dr. Peter Panus for inviting me to join the team. It's been my honor to serve as part of the UCSF Cellular and Molecular Pharmacology department. I am deeply grateful to my pharmacology mentors, Dr. Susan B. Masters, Dr. Anthony J. Trevor, and above all Dr. Bert G. Katzung. They shared with me their passion for pharmacology and for teaching. They inspire me every day to do my best in the classroom and in our textbooks. I thank the numerous students for their insightful questions, which pushed me to become a better educator. Finally, I thank my husband Carl T. Hall for his support and advice.

—Marieke Kruidering-Hall

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PART I BASIC PRINCIPLES

CHAPTER 1

Introduction

Pharmacology is the study of substances that interact with living systems through chemical processes, especially by binding to regulatory molecules and activating or inhibiting normal body processes. In this book, these substances will usually be referred to as *drugs*. Medical pharmacology, or pharmacotherapeutics, is the use of drugs to achieve a beneficial therapeutic effect on some process within the patient or to promote toxic effects on the regulatory processes in organisms that are infecting the patient. Pharmacotherapeutics may be further subdivided into pharmacodynamics and pharmacokinetics. Pharmacodynamics (Chapter 2) evaluates the effect of the substance on biologic processes—or, the "effect of the *drug* on the *body*." Pharmacokinetics (Chapter 3) examines the absorption, distribution, and elimination of substances—or, the "effect of the *body* on the *drug*." Toxicology is the branch of pharmacology that deals with the undesirable effects of chemicals on individual cells and humans (medical toxicology) all the way up to their negative effects on complex ecosystems (environmental toxicology).

Humans have been using substances for their medicinal value throughout history. The earliest written records from China and Egypt list many remedies derived from plants and animals, including a few still recognized today as useful drugs. Most, however, were of limited clinical value or were actually harmful. Near the end of the 17th century, observation and experimentation began to replace theorizing in physiology and medicine. In the late 18th and early 19th centuries, experimental animal physiology and advances in chemistry further increased understanding of how chemical substances had their effects at the organ and tissue levels. Eventually, these discoveries led to the concept of drug selectivity in which a drug's action is related to its structure because of how it *specifically* binds to a receptor. Also recognized at this time was that drugs could be grouped together into pharmacologic classes based on their chemical structure or physiologic effect. About 60 years ago, a major expansion of research efforts in all areas of biology began. This expansion coincided with the systematic development of controlled clinical trials that allow accurate evaluation of the therapeutic value of drugs. As new concepts and techniques have been introduced, information has accumulated about the action of drugs on their specific receptors. Many fundamentally new classes of drugs as well as new members of old classes have been introduced. Though still in its infancy, the field of pharmacogenomics will likely herald a new era of pharmaceutical intervention in which the knowledge of an individual's response to drugs based on his or her genes will enable tailoring of medications and dosages to allow more effective medications with ever-safer profiles.

The extension of scientific principles into everyday pharmacotherapeutics is still ongoing. Unfortunately, the drug-consuming public is also exposed to vast amounts of inaccurate, incomplete, or unscientific information regarding the pharmacologic effects of drugs. This has resulted in the faddish use of innumerable expensive, ineffective, and sometimes harmful remedies and the growth of a huge "alternative healthcare" industry. A lack of understanding of basic scientific principles, the investigative process, and statistics has led to rejection of medical pharmacology by a segment of the public, and a common tendency to assume that all adverse drug effects are the result of malpractice. Two general principles should form the basis of understanding for the evidence-based use of drugs. First, *all* substances may, under certain circumstances, be toxic. Second, *all* therapies promoted as health enhancing should meet the same standards of evidence of efficacy and safety. There should

be no artificial separation between evidence-based medicine and "alternative" or "complementary" medicine.

To learn every pertinent fact about every drug would be impractical for the physical therapist. Fortunately, this is also unnecessary because almost all of the several thousand drugs currently available may be arranged in about 70 pharmacologic classes. Many of the drugs within each class are very similar in pharmacodynamic actions and often in their pharmacokinetic properties as well. For most pharmacologic classes, one or more prototypic drugs may be identified that typify the key characteristics of the class. This permits classification of other important drugs in the class as variants of the prototype, so that only the prototype must be learned in detail; for the remaining drugs, only the differences from the prototype need to be learned.

THE NATURE OF DRUGS

In the most general sense, a drug may be defined as any substance that brings about a change in biologic processes through its chemical actions. Commonly used drugs include inorganic ions, nonpeptide organic molecules, small peptides and proteins, nucleic acids, lipids, and carbohydrates. Although proteins (eg, insulin) have been used as drugs for decades, recently the term "biologicals" has come to represent proteins that are commercially produced in prokaryotic or eukaryotic cell lines using recombinant DNA technology (eg, recombinant human insulin, or rh insulin). Poisons have almost exclusively detrimental effects, but they may also be used clinically as drugs. For example, foxglove (*Digitalis purpurea*) is a plant found in many flower gardens that is considered toxic when consumed. However, an extract from the leaves of the plant yields digoxin, a therapeutic cardiac glycoside (Chapter 9). Toxins are usually defined as poisons of biologic origin that are synthesized by plants or animals. Rarely, toxins may also be used as drugs. The most obvious example is botulinum toxin. Botulinum toxin is a potent exotoxin produced by the bacterium *Clostridium botulinum* as a result of inappropriate food canning for preservation. Now, botulinum toxin is used clinically for many conditions as a selectively injected skeletal muscle relaxant. Finally, though not traditionally thought of as drugs, pieces of genetic material can be manipulated to alter intracellular targets. The discovery that small segments of RNA may selectively interfere with protein synthesis has led to the clinical application of small interfering RNAs (siRNAs) and microRNAs (miRNAs). Similarly, short nucleotide chains called antisense oligonucleotides that are complementary to RNA or DNA can interfere with gene expression and RNA transcription.

A drug is often administered at a location distant from its intended site of action. For example, a tablet or capsule is taken orally to relieve a headache. Therefore, a clinically applicable drug must have the necessary properties to be transported from its site of administration to its site of action. The drug should also be inactivated or excreted from the body at a reasonable rate so that its actions will be of a desired duration. In the majority of cases, the drug interacts with a specific molecule called a receptor that plays a regulatory role. In order to interact chemically with its receptor, a drug molecule must have the appropriate size, electrical charge, shape, and atomic composition.

At room temperature, a drug may be a solid, liquid, or gas. These physical factors often determine the best route of administration. Many drugs are weak acids or weak bases. Drugs vary in size from a small ion (eg, lithium cation) to a large protein (eg, tissue-plasminogen activator). In order to have a good "fit" to only one type of receptor, a drug molecule must be sufficiently unique in shape and charge and other physical properties to prevent binding to other receptors. In contrast, drugs that are too large will not diffuse readily between compartments of the body.

Rational Drug Design

Rational design of drugs implies the ability to predict and then construct the appropriate molecular structure of a drug on the basis of information about its biologic receptor. Until recently, no receptor was known in sufficient detail to permit such drug design. Instead, drugs were developed through random testing of chemicals or modification of drugs already known to have some effect. However, during the past three decades, many receptors have been isolated and characterized. A few drugs now in use were developed through molecular design based on knowledge of the three-dimensional structure of the receptor site. As more receptor structures are systematically identified, rational drug design will become more frequent.

NEW DRUG DEVELOPMENT

Preclinical Development

By federal law, the safety and efficacy of drugs must be determined *before* they are marketed in the United States. The development of new drugs is a multistep process requiring molecular, cellular, animal, and human clinical trials prior to governmental approval and marketing (**Figure 1-1**). New drugs may be developed in different ways. They may be developed through investigation of chemical structure or biologic mechanisms, or based on the actions of known drugs. Alternatively, drugs may be developed from screening a large number of biologically derived or synthesized substances. Regardless of the source or the key idea leading to a candidate drug molecule, testing a new drug involves a sequence of experimentation and characterization called drug screening. A variety of biologic assays at the molecular, cellular, organ, and whole animal levels are used to define the activity and selectivity of the drug. The molecule is studied for a broad array of actions to establish its mechanism of action and selectivity. These assays, especially at the whole animal level, may demonstrate unsuspected toxic effects and occasionally disclose a previously unsuspected therapeutic action. Research efforts may result in a candidate molecule, called a lead compound, which is then investigated further. At this juncture, the company or university that performed the preclinical

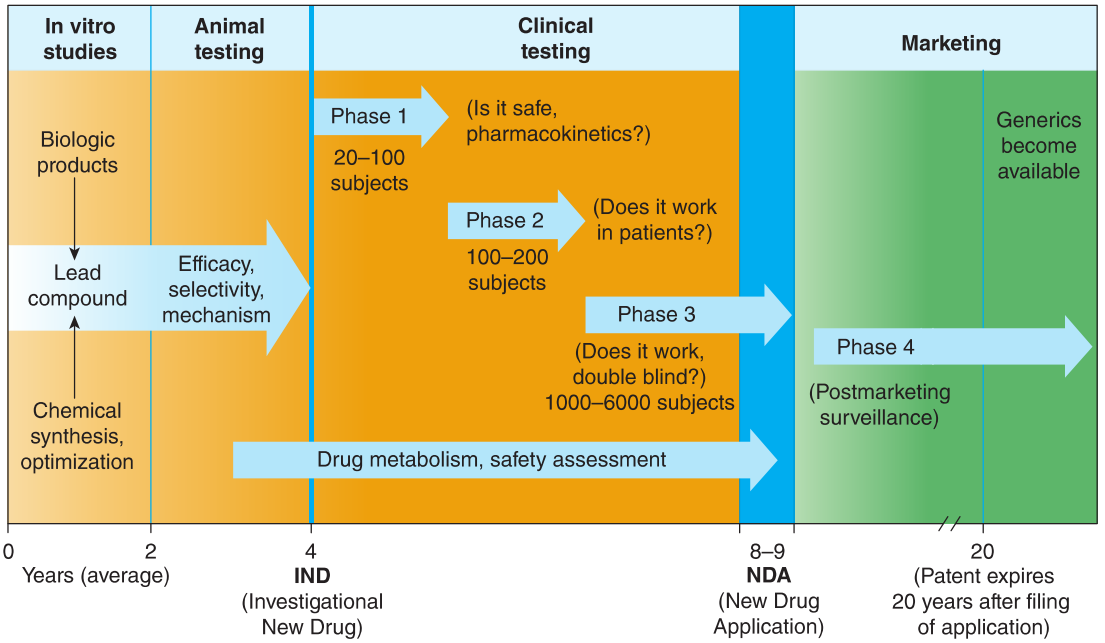

FIGURE 1-1 The development and testing process required to bring a drug to market in the United States. Some of the requirements may be different for drugs used in life-threatening diseases.

research may file a patent application for an effective novel compound or for a new and nonobvious therapeutic use for a previously known drug.

As part of the preclinical investigative process, lead compounds are evaluated for clinical potential. Table 1-1 lists several toxicity tests conducted during this phase. The precise sequence of tests is determined following deliberation by the Food and Drug Administration (FDA) and the applying entity. The goal of these investigations is to be able to estimate the risk associated with exposure to the drug under specified conditions. It is important to realize that no drug can be certified as completely free of risk since every drug is toxic at some dosage. In addition to the safety tests shown in Table 1-1, several quantitative estimates conducted during these preclinical investigations are required and are discussed in Chapter 3.

Due to the urgent need in treating life-threatening diseases, certain drugs require less preclinical evidence of safety. For example, some anticancer or anti-infective drugs are investigated and approved on an accelerated schedule.

Clinical Evaluation in Humans

Less than one-third of the drugs that are tested in clinical trials reach the marketplace. Federal law requires that the study of new drugs in humans be conducted in accordance with stringent guidelines. The FDA is the administrative body that oversees the drug evaluation process and grants approval for marketing of new drugs in the United States. The FDA's authority to regulate drug marketing is derived from federal legislation. To receive approval by the FDA for marketing, a drug

TABLE 1-1 Safety tests conducted in animals.

Type of Test	Comment
Acute toxicity	Usually two species and two routes. Determine doses at which there is no toxicity and maximum tolerated dose. In some cases, determine the acute dose that is lethal in approximately 50% of animals.
Subacute toxicity	Three doses and two species with physiologic and biochemical effects examined. Duration is dependent on length of clinical use. The longer the intended clinical use, the longer the duration of testing.
Chronic toxicity	Rodent and one additional non-rodent species for ≥ 6 months. Required if clinical application for the drug is anticipated to be chronic.
Carcinogenic potential	Two-year duration and in at least two animal species. Conducted when drug is intended for prolonged clinical use.
Reproductive performance effect	To test effects on animal mating behavior, reproduction, parturition, progeny, birth defects, and postnatal development. Conducted in two species (usually one rodent and rabbits).
Mutagenic potential	Examines genetic stability and the potential for mutations in prokaryotic and eukaryotic organisms.

must be demonstrated to be "safe and efficacious" through experimental investigation. Unfortunately, "safe" means different things to the patient, the physician, and society. A complete absence of risk is impossible to demonstrate, but this fact is not well understood by the average member of the public, who assumes that any drug sold with FDA approval must be free of serious "side effects." Obviously, it is impossible to certify that a drug is absolutely safe for every person at every dosage. Experimental investigation can identify most of the hazards likely to be associated with use of a new drug and place some statistical limits on the frequency of occurrence of such events in the population under study. As a result, an operational and pragmatic definition of "safety" can usually be reached that is based on the nature and incidence of drug-associated hazards compared with the hazard of nontherapy for the target disease. However, the frequent mismatch between unrealistic expectation of "safety" and scientific determination of adverse event probability continues to be a major cause of litigation and dissatisfaction with medical care.

Clinical Trials

The new drug approval process involves a systematic series of investigations. Once a lead compound is judged ready to be studied in humans, the originating university or company files a Notice of Claimed Investigational Exemption for a New Drug (IND) and the FDA must approve the proposed clinical studies before any testing can occur in humans (Figure 1-1).

In phase 1, the dose-dependent effects of the drug are established in a small number (20-100) of healthy volunteers. Phase 1 trials are done to determine whether humans and animals show significantly different responses to the drug, and to establish the probable limits of the safe clinical dosage range. Note that *efficacy* cannot be determined in phase 1 because the volunteer subjects do not have the target disease for which the drug is being evaluated. Pharmacokinetic parameters (Chapter 3) are often established in phase 1.

In phase 2, the drug is administered for the first time to determine its efficacy in patients with the target disease. A small number of patients (100-200) are studied in great detail to evaluate the drug's therapeutic benefits and a broader range of its toxicities. If the drug is expected to have significant toxicities, as is often the case in cancer and anti-infective therapy, volunteer patients with the disease are used. This design is designated as a phase 1/2 study.

In phase 3, the drug is evaluated in a much larger sample size to establish safety and efficacy under conditions of its proposed use. Phase 3 clinical trials can be difficult to design and execute, and are usually very expensive because of the large numbers of patients involved and the amount of data that must be systematically collected and analyzed.

During phases 2 and 3, the clinical efficacy of the investigational new drug is typically compared to a placebo or an alternative drug (ie, current standard therapy for the clinical condition). Phase 2 trials utilize single blinding or double blinding, in which the patient or the patient and the treating physician are unaware of whether the experimental drug is being administered. In double-blind trials, a third party not involved in the experimental procedure is responsible for holding the code that identifies each drug sample; this code is only broken when all clinical data have been collected. All phase 3 clinical trials are double blind. Often, 4-6 years of clinical testing are needed to accumulate enough data. Chronic safety testing in animals is usually done concurrently with clinical trials. In all three formal phases of clinical trials, volunteers or patients must be informed of the investigational status of the drug as well as possible risks. They must be allowed to either decline or consent to participate in the research process and provide written informed consent prior to participation.

If the results from the animal and human studies meet expectations, the drug manufacturer must submit a New Drug Application (NDA)—or, for biologicals, a Biological License Application (BLA)—to the FDA prior to marketing the new drug (Figure 1-1). If the FDA approves the NDA, the drug manufacturer in conjunction with the FDA develops a "label" for the drug. This label describes the specific medical condition treated by the drug (ie, the condition for which the drug was tested in clinical trials), adverse effects of the drug, and appropriate dosages for the drug. After the drug has been approved and marketed, it may be prescribed for other medical conditions not listed on the label. Such usage is the drug's "off-label" use. In cases where an urgent need is perceived, the process of preclinical and clinical testing and FDA review may be greatly accelerated. For serious diseases, the FDA can permit extensive but controlled marketing of a new drug before phase 3 studies are completed.

Once marketing of a drug has commenced, phase 4 or postmarketing surveillance begins. This phase constitutes monitoring the safety of the new drug under actual conditions of use in large numbers of patients. While phase 4 has no fixed duration and has not been as rigidly regulated by the FDA, its importance should not be underestimated. Careful monitoring by physicians prescribing the new drug provides valuable data regarding adverse effects that occur at a low incidence rate that may not have been detected in the smaller sample sizes of the phases 1, 2, and 3 studies.

The time from the filing of a patent application to approval for marketing of a new drug can be 5 years or considerably longer. Since the lifetime of a patent is 20 years in the United States, the owner of the patent, usually a pharmaceutical company, has exclusive rights for marketing the product for only a limited time after approval of the NDA. Because the FDA review process can be lengthy, the time consumed by the review process is sometimes added to the patent life. However, the extension (up to 5 years) cannot increase the total life of the patent to more than 14 years after NDA approval. After the patent expires, any company may produce a bioequivalent that has similar content, purity, and bioavailability and market this compound as a generic drug, without paying license fees to the original patent owner. The FDA drug approval process is one of the rate-limiting factors in the time it takes for a drug to be released to the market and used by patients.

ADVERSE DRUG REACTIONS

As discussed in later chapters, all drugs interact in specific ways with living systems. In part, the specificity of these interactions dictates the range of effects on these systems. As such, some interactions result in *unintended* physiologic reactions. No drug, whether prescribed, over-the-counter, or procured in another form (eg, vitamin, herbal product, or supplement), is completely without the potential for unintended physiologic reactions. The term "side effect" is often used to indicate *any* unintended effect that a drug may have. However, some unintended reactions may go unnoticed or are not bothersome to the patient, whereas other reactions are deleterious to the patient. The latter are described as adverse drug reactions (ADRs) or adverse drug events (ADEs). Since most physical therapists are not prescribers but have more pharmacology knowledge than the typical layperson, use of the term "ADR" or "ADE" may be preferred over "side effect" for two reasons. First, physical therapists are primarily concerned with harmful unintended drug reactions that may be detrimental to rehabilitation goals. Second, preferential use of the term "ADR" or "ADE" with other healthcare professionals helps set the stage for interprofessional communication regarding patient compliance with medications and suspected ADRs that may be limiting rehabilitation progress.

Severe ADRs to marketed drugs are uncommon; life-threatening reactions probably occur in less than 2% of patients admitted to medical wards. Less dangerous toxic effects, as noted elsewhere in this book, are frequent for some pharmacologic classes. Mechanisms of these ADRs fall into two main categories. The first category is often an extension of known pharmacologic effects and thus is predictable. Predictable toxicities are generally discovered during phases 1 through 3 of testing. The second category, which might be immunologic in origin or of unknown mechanism, is frequently unexpected and often not recognized until a drug has been marketed for some years. These toxicities are therefore usually discovered after marketing (phase 4). Thus, healthcare professionals should be aware of the various types of allergic reactions to drugs.

CHAPTER 1 QUESTIONS

1. Which of the following describes the undesirable effects of chemicals on living systems?

   a. Toxicology
   b. Pharmacology
   c. Pharmacodynamics
   d. Pharmacokinetics

2. Which of the following is a chemical that is synthesized by a plant or animal and is also detrimental to biologic processes?

   a. Toxin
   b. Poison
   c. Drug
   d. Biological

3. Which of the following federal agencies oversees drug evaluation and marketing in the United States?

   a. Drug Enforcement Agency (DEA)
   b. National Institutes of Health (NIH)
   c. United States Department of Agriculture (USDA)
   d. Food and Drug Administration (FDA)

4. Which of the following must be filed prior to clinical human studies?

   a. New Drug Application (NDA)
   b. Investigation Exemption for a New Drug (IND)
   c. Label of Research (LOR)
   d. Program Project Grant (PPG)

5. The process of applying for marketing approval for a new drug is an NDA.

   a. True
   b. False

6. What is the maximum lifetime of a patent on a drug in the United States?

   a. 4 years
   b. 10 years
   c. 15 years
   d. 20 years

7. Which clinical research phase involves the largest number of human research subjects and is double blinded?

   a. Phase 1
   b. Phase 2
   c. Phase 3
   d. Phase 4

8. Once a drug receives an NDA, the manufacturer is not required to continue monitor the drug for safety.

   a. True
   b. False

9. If a drug is expected to have significant toxicity, phases 1 and 2 may be combined.

   a. True
   b. False

10. Which of the following identifies the clinical use of a drug other than what the FDA provided the NDA for?

    a. Label
    b. Off-label
    c. Prescription
    d. Tag

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CHAPTER 2

Pharmacodynamics

REHABILITATION FOCUS

It is estimated that medications are involved in up to 80% of all treatments and impact every aspect of a patient's life. As a result, physical therapists must recognize that drugs may alter a patient's clinical presentation, which at times may require that physical therapy interventions be modified. Knowledge of drug classes and their mechanisms of actions is key to understanding patients' responses to medications. The beneficial clinical effects of drugs occur within specific concentration ranges. These ranges are unique to the different pharmacologic classes of drugs and, for some drugs, unique to the specific individual. Concentrations *below* the effective range provide no therapeutic benefit, while concentrations *above* the range almost always result in adverse drug reactions (ADRs). As discussed in the Chapter 3, the goal of dosing regimens is to utilize knowledge of the therapeutic range for each drug to determine the frequency and dose for a specific person.

Both the therapeutic and toxic effects of the majority of drugs result from interactions with their specific molecular targets—receptors. A drug molecule is an exogenous ligand that interacts with a receptor and initiates a chain of biochemical and physiologic events leading to the drug's observed effects. Pharmacodynamics is the branch of pharmacology concerned with the interaction between drug and receptor and the subsequent results.

A drug's mechanism of action is based on whether it mimics or inhibits an endogenous ligand or has some other unrecognized effect(s). A drug may directly compete with an endogenous ligand for a specific receptor or modulate the affinity (binding strength) of the receptor for the endogenous ligand. Some drugs may permanently inactivate the receptor to which they bind or stimulate additional cellular homeostatic mechanisms, which can result in a clinical effect lasting after the drug itself is no longer present in the body.

Key principles underlying the receptor concept form the basis of understanding the actions and clinical uses of drugs. These principles also have important practical consequences for drug development. First, receptors largely determine the quantitative relationship between dose or concentration of a drug and its pharmacologic effects. The receptor's affinity for binding a drug determines the concentration of drug required to form a significant number of drug-receptor complexes. In addition, the total number of receptors may limit the maximal effect a drug may produce. Second, receptors are responsible for the *selectivity* of drug action. The molecular size, shape, and electrical charge of a drug determine whether it will bind to a particular receptor among the vast array of chemically different binding sites available within the body. Accordingly, changes in a drug's chemical structure can dramatically alter its affinity for different classes of receptors, with resulting alterations in therapeutic and toxic effects. Finally, receptor activation (by agonists) or receptor blockade (by antagonists) are the primary factors responsible for many clinical effects of drugs. Knowledge of whether a drug is an agonist, antagonist, or partial agonist makes it possible to understand the actions of a drug, an individual's physiologic responses to a drug, a drug's potential ADRs, as well as interactions with many other drugs.

DRUG-RECEPTOR BONDS

Receptors are specific molecules that drugs interact with to produce changes in cellular function, and ultimately to produce functional changes in the whole person. Most receptors are proteins. A few receptors are macromolecules such as DNA. Enzymes that are affected by drugs are also considered receptors.

In order to respond to *specific* chemical stimuli, receptors must be selective in their ligand-binding characteristics. The receptor site presents a unique three-dimensional configuration upon which the drug can bind. The complementary configuration of the drug is in part what creates the affinity of the drug for the receptor site (**Figure 2-1**). Drugs that bind to a limited group of receptor types may be classified as selective, whereas drugs that bind to a larger number of receptor types may be considered nonselective.

Drugs interact with receptors by means of chemical bonds. The three major types of bonds are covalent, electrostatic, and hydrophobic. Covalent bonds are strong and in many cases not reversible under biologic conditions. Electrostatic bonds are weaker, more common, and often reversible. Hydrophobic bonds are the weakest, and probably most important in the interactions of lipid-soluble drugs, and within hydrophobic "pockets" of receptors.

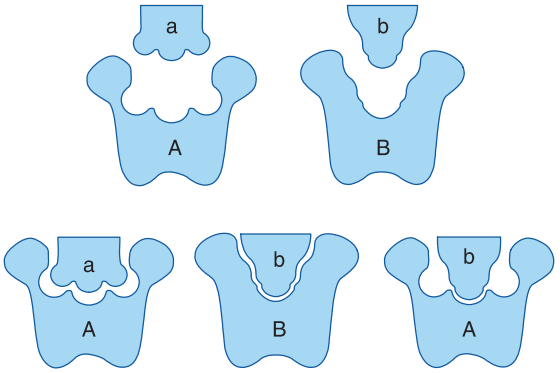

FIGURE 2-1 Model of specificity of a drug for the receptor. The structure of drug "a" allows binding only to receptor "A." In contrast, the structure of drug "b" allows binding to either receptor "A" or "B." Drug "a" would be considered selective to receptor "A," while drug "b" would be considered nonselective.

DOSE-RESPONSE CURVES

Graded Dose-Response Relationships

In order to initiate a sequence of cellular events that ultimately results in physiologic and clinical responses, a drug or an endogenous ligand (eg, hormone or neurotransmitter) must bind to a specific receptor. The response induced by activation of this receptor system can be measured against the concentration (dose) and displayed in a graded dose-response curve (Figure 2-2A). Plotting the data with a logarithmic dose axis usually results in a sigmoid curve, which simplifies the manipulation and interpretation of the dose-response data (Figure 2-2B).

The concentration of a drug required to achieve 50% of the maximal response is called the EC_{50}. For some ligands, the EC_{50} also estimates the drug concentration that binds 50% of available receptors. Thus, the dose-response curve relates the binding of the drug to the receptor (ie, the affinity of the drug for the receptor). A drug's efficacy is its ability to produce a measurable response, which is primarily determined by the nature of the drug and its receptor and associated effector system. The minimal effective dose is the concentration below which a drug produces no clinical benefit. At higher concentrations, the maximal efficacy of the drug (maximal effect; E_{max}) will be reached and no additional beneficial clinical response is observed.

Quantal Dose-Response Relationships

When the minimum dose required to produce an intended magnitude of response is evaluated for a *population*, a quantal dose-response relationship may be determined. When the fraction of the population that responds at each dose is plotted against the log of the dose administered, a cumulative quantal dose-response curve is obtained (Figure 2-3). From this curve, several clinically important doses can be determined. These include the median effective dose (ED_{50}) and the median toxic dose (TD_{50}). In preclinical animal studies, the median lethal dose (LD_{50}) is also calculated. Two key safety characteristics may also be determined: the therapeutic index and the therapeutic window. The therapeutic index is calculated by dividing the TD_{50} (or LD_{50}) by the ED_{50}. A very safe drug might be expected to have a very large toxic dose and a much smaller effective dose; thus, a safe drug would have a relatively high therapeutic index. Unfortunately, varying slopes for the dose-response plots sometimes make the therapeutic index a poor measure of safety. An alternative and potentially more clinically useful safety index is the therapeutic window. The therapeutic window is the dosage range between the minimum effective dose and the minimum toxic dose.

Potency

Potency is defined as the amount of drug needed to produce a given effect. Potency can be determined from either graded dose-response curves or quantal dose-response curves; however, the obtained values are not identical. In graded dose-response curves, potency is characterized by the EC_{50}

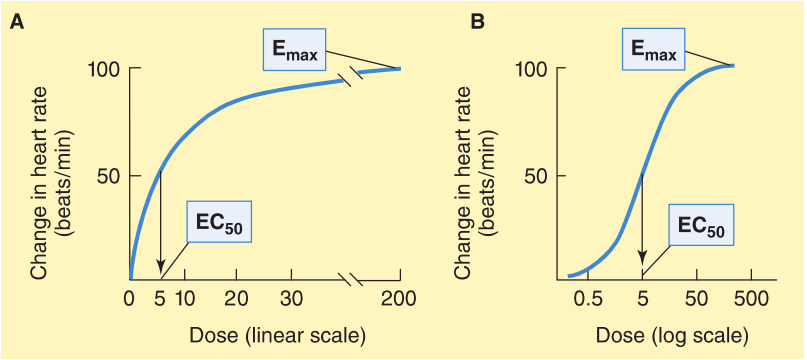

FIGURE 2-2 Graded dose-response graphs in which drug dose or concentration is plotted against a chosen clinical effect (change in heart rate). The EC_{50} is the dose of a drug at which the effect is half-maximal. The E_{max} is the dose of a drug at which the maximal beneficial clinical response is produced. When the dose axis is linear **(A)**, a hyperbolic curve is commonly obtained; when the dose axis is logarithmic **(B)**, a sigmoidal curve is often obtained.

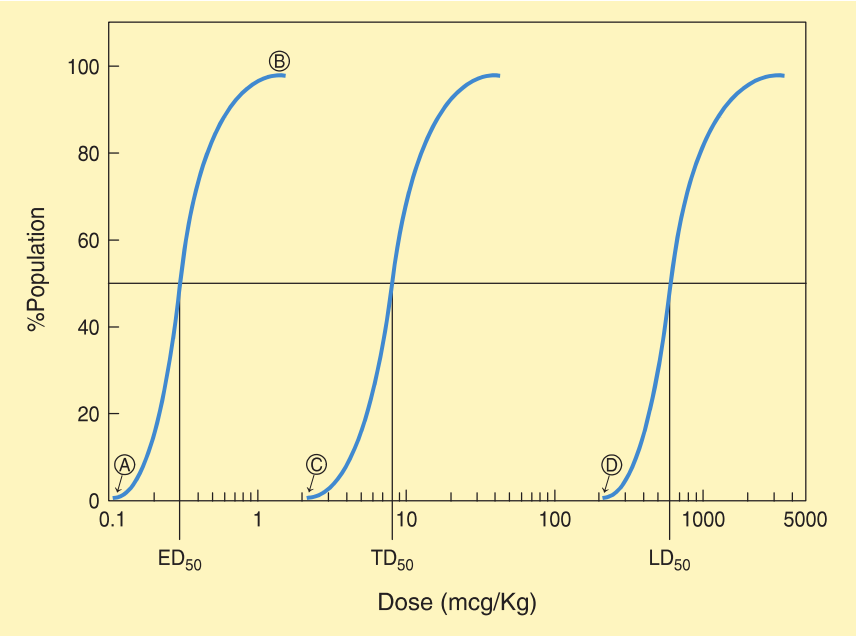

FIGURE 2-3 **Quantal dose-response plot.** The curves are generated from the frequency distribution of doses of a hypothetical drug required to produce a specified effect. The median effective dose (ED_{50}), median toxic dose (TD_{50}), and median lethal dose (LD_{50}) are depicted. A: minimal effective dose (MED; 0.1 mcg/kg). B: maximal effective dose (1.5 mcg/kg). C: minimal toxic dose (MTD; 2.0 mcg/kg). D: minimal lethal dose (200 mcg/kg). The therapeutic index is calculated by dividing the TD_{50} (8 mcg/kg) by the ED_{50} (0.3 mcg/kg) to obtain approximately 27. The therapeutic window is the range between the MED (A) and the MTD (C), which is 0.1-2 mcg/kg.

(Figure 2-2). The smaller the EC_{50}, the greater the potency of the drug. In quantal dose-response curves, the ED_{50}, TD_{50}, and LD_{50} measurements are identified as the potency variables (Figure 2-3).

DRUG-RECEPTOR DYNAMICS

Full Agonists, Partial Agonists, and Inverse Agonists

Figure 2-4 illustrates the modern two-state receptor theory, which considers the receptor to have at least two states: active (R_a) and inactive (R_i). In the absence of ligand, a receptor might be completely inactive or fully active. Alternatively, an equilibrium state might exist with most receptors in the inactive state and some receptors in the activated state (R_i + R_a). Many receptor systems exhibit some activity in the *absence* of a ligand, suggesting that some fraction of the receptor population is always in the activated state. This type of activity in the absence of ligand is called constitutive activity.

A full agonist is a drug (or endogenous ligand such as a neurotransmitter or hormone) that is capable of fully activating the effector system upon binding to the receptor. In the model system illustrated in Figure 2-4, a full agonist drug (D_a) has high affinity for the activated receptor conformation (R_a), and sufficiently high drug concentrations result in all the receptors achieving the activated state (R_a – D_a). In contrast, a partial agonist produces less than the full effect, even when it has saturated the receptors (R_a-D_{pa} + R_i-D_{pa}), presumably by combining with both receptor conformations, but favoring the active state. In the presence of a full agonist, a partial agonist actually acts as an inhibitor. In this model, neutral antagonists bind with *equal* affinity to the R_i and R_a states, preventing binding by an agonist and preventing any deviation from the level of constitutive activity. In contrast, inverse agonists have a higher affinity for the inactive R_i state than for R_a and decrease or abolish any constitutive activity (R_i – D_i).

Full agonists demonstrate both affinity and maximal efficacy for the receptors that ultimately result in the physiologic response(s). A partial agonist binds to the receptor at the same location as the full agonist. However, the partial agonist achieves a *lower* maximal effect, even with full receptor occupancy (Figure 2-5). By definition, partial agonists have a lower maximal efficacy than full agonists, and in the presence of full agonists, they may inhibit the full agonists, decreasing their response.

A concept worth emphasizing is the distinction between a drug's potency and its efficacy. Figure 2-5 presents two full agonists (A and B) that produce equal and maximal efficacy. However, agonist B has a lower affinity for the receptor compared to A. As a result of this binding difference, agonist A is described as having a higher potency compared to B because a lower dose of A is needed to achieve the same effect. The partial agonist C demonstrates a lower maximal efficacy than either of the full agonists (A or B), yet has a higher potency than either of the full agonists. Thus, potency and efficacy are not interchangeable. In other words, one drug may have a higher potency and a lower maximal efficacy than another drug that acts at the same receptor.