Psychopharmacology 4e

by Meyer, Farrar, Biezonski and Yates

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Meyer
Farrar
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Psychopharmacology

FOURTH
EDITION

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Psychopharmacology

Drugs, the Brain, and Behavior

Fourth Edition

Jerrold S. Meyer ▪ Andrew M. Farrar
Dominik Biezonski ▪ Jennifer R. Yates

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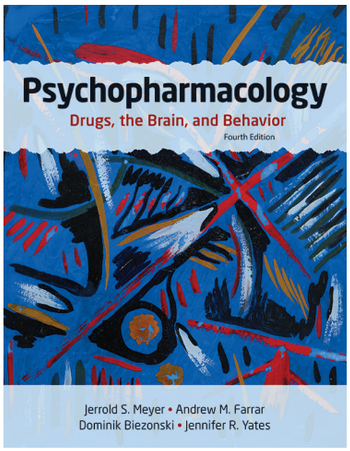

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Anonymous, *Mescaline Painting – Blue and Red Abstract* (c. 1938). This striking painting was a product of a 1930s British psychiatric experiment to study artistic self-expression under the influence of mescaline, which at the time was purported to induce a schizophrenia-like state. Courtesy Bethlem Museum of the Mind.

Psychopharmacology
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Jerrold Meyer *dedicates his contribution to the book to his lovely wife and colleague, Dr. Melinda Novak, for her unwavering patience and support during the countless hours he was squirreled away in his home office working on the project.*

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Brief Contents

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Preface

Jerrold Meyer and Linda Quenzer were approached by Sinauer Associates about 20 years ago to develop a new undergraduate textbook on psychopharmacology. We were already co-authors with Robert Feldman on a massive, 900-page-long graduate level textbook entitled *Principles of Neuropsychopharmacology*, but our Sinauer editor wanted something more than just a condensed and simplified version of the "big book." Our charge was to engage the interest of undergraduate students in learning about psychoactive drugs and their mechanisms of action, while maintaining the more advanced textbook's high standard of comprehensive and up-to-date coverage. The fact that Sinauer has now published the Fourth Edition of *Psychopharmacology: Drugs, the Brain, and Behavior,* indicates that we have had some success in fulfilling that charge.

In the preface to the first edition of this work, the authors commented on the long history of human use of mind-altering substances that eventually led to the need for a science of psychopharmacology. This field of study was already exploding by the late 20th and early 21st centuries, and nothing has happened since then to slow down this remarkable growth. However, new trends are always emerging in any vibrant area of scholarship, and psychopharmacology is no exception in that regard. One such trend particularly worth noting is the impact of changing attitudes toward formerly disparaged substances, at least within Western societies. This impact can be seen in two significant developments. First, many countries or smaller political districts (i.e., states, provinces, or cities), especially within North America and Western Europe, are decriminalizing the personal use of various recreational drugs. Some drugs, like cannabis, have even been fully legalized for such use. Although the politics of decriminalization and legalization remain contentious, a clear trend is in place. Second, we are seeing a remarkable development of therapeutic applications using mind-altering drugs like psilocybin, LSD, MDMA (ecstasy), and ketamine, that until recently were deemed highly addictive and (except for ketamine) without legitimate medical use. Again, this development is not without controversy; however, we are convinced that the growing empirical evidence for therapeutic benefits derived from careful use of psychedelic medications will cement their place in the therapeutic domain.

In accordance with pharmacology being a medical discipline, this new edition continues to emphasize the known or potential therapeutic applications of every compound mentioned in the textbook. However, it's important for readers to recognize not only the advances being made in medications development for some CNS disorders, but also the areas where progress has been frustratingly slow. For example, the introduction of new and exciting psychedelic medications promises to benefit mood-, anxiety-, and trauma-related disorders, but these drugs are less likely to help patients recover from neurodegenerative disorders like Alzheimer's disease, multiple sclerosis, or amyotrophic lateral sclerosis. Drug addiction and autism spectrum disorders are two other important areas where advances in pharmacotherapy have lagged. Therefore, throughout the book we have tried to identify the specific therapeutic benefits and limitations (where appropriate) of each successful medication, failures of medications that seemed promising at one time, and gaps where new medications are sorely needed.

Every chapter in this Fourth Edition is fully updated, with many citations from 2020 and 2021. Special attention is given to recent developments and emerging trends in psychopharmacology while retaining the same organization as in previous editions. The first four chapters provide extensive foundation materials, including the basic principles of pharmacology, neurophysiology and neuroanatomy, cell signaling in the nervous and endocrine systems, and current methods in behavioral assessment and neuropharmacology. The new Case Studies box feature is used in Chapter 1 (Principles of Pharmacology) and in Chapter 2 (Structure and Function of the Nervous System) to demonstrate how the basic concepts of pharmacology and neuroscience are applied in clinical practice. Among the highlights of Chapter 3 (Chemical Signaling by Neurotransmitters and Hormones) are expanded coverage of oxytocin and vasopressin regulation of social behaviors and current evidence on the use of oxytocin to treat the social communication deficits present in autism spectrum disorder. Chapter 4 (Methods of Research in Psychopharmacology) is updated with examples of state-of-the-art techniques, including examples from genetic engineering and artificial intelligence, to illustrate how these technologies are being used to better understand drug effects on behavior and the complex

genetic basis of drug-organism interactions. The next four chapters, Chapter 5 (Catecholamines), Chapter 6 (Serotonin), Chapter 7 (Acetylcholine), and Chapter 8 (Glutamate and GABA), describe the key features of neurotransmitter systems that are particularly important to psychopharmacologists. Information about the neurochemistry, anatomy, and behavioral functions of these transmitters not only lays the groundwork for the chapters that follow, but this new edition places increased emphasis on clinical applications of neurotransmitter-targeted drugs. The next eight chapters focus on recreational drugs and their potential for misuse. Chapter 9 (Drug Misuse and Addiction) covers the current theories and mechanisms of drug addiction, which is followed by seven chapters devoted to specific recreational drugs. Chapter 10 (Alcohol) discusses the pharmacology of alcohol, the features of alcohol use disorder (previously called alcoholism), and both current and emerging treatments for this disorder. Chapter 11 (The Opioids) describes the features of the endogenous opioid system, opioid use disorder, and novel treatments for that disorder. The chapter has been updated to reflect the increasing severity of the opioid epidemic and the array of harm-reduction strategies being employed to combat it. This section of the book continues with Chapter 12 (Psychomotor Stimulants: Cocaine, Amphetamine, and Related Drugs), Chapter 13 (Nicotine and Caffeine), Chapter 14 (Marijuana and the Cannabinoids), Chapter 15 (Psychedelic and Hallucinogenic Drugs, PCP, and Ketamine), and Chapter 16 (Inhalants, GHB, and Anabolic-Androgenic Steroids). Among the highlights of these chapters are greatly expanded coverage of e-cigarettes and vaping (Chapter 13), new discussions of cannabis legalization and emerging therapeutic applications of cannabidiol (CBD) and other cannabinoids (Chapter 14), and the mechanisms by which entactogens and psychedelic drugs (MDMA, psilocybin, and LSD) are thought to work when used in drug-assisted psychotherapy for mood- and trauma-related disorders (Chapter 15). The final four chapters consider the neurobiology of neuropsychiatric and neurodegenerative disorders and the drugs used to treat these disorders. Chapter 17 (Disorders of Anxiety and Impulsivity and the Drugs Used to Treat Them) and Chapter 18 (Affective Disorders: Antidepressants and Mood Stabilizers) cover not only classical pharmacotherapies such as benzodiazepines and selective serotonin reuptake inhibitors (SSRIs) but also novel approaches using more "non-traditional" substances such as ketamine and psilocybin, that are discussed in prior chapters on recreational drugs. We highlight ongoing studies on these substances that seek to determine optimal dosing regimens, tolerability, durability, and mechanisms of action, the latter which may lead to the generation of novel compounds with reduced side effects. Chapter 19 (Schizophrenia: Antipsychotic Drugs) has been updated with examples of recent studies demonstrating the promise of pharmacogenetics in optimizing treatment efficacy while reducing side effects, such as tardive dyskinesia. Finally, Chapter 20 (Neurodegenerative Diseases) updates our discussion of the symptoms, clinical trials, FDA-approved therapies, and diagnostic tools, including advances in neuroimaging, for all disorders covered in the chapter. It additionally introduces novel developments such as a new symptom (unusual body odor) that helps diagnose Parkinson's disease and a recently developed technology (focused ultrasound) for treating Alzheimer's disease.

Several features of *Psychopharmacology: Drugs, the Brain, and Behavior* distinguish it from its many competitors. Full-color photos depict pharmacologically relevant plant species, drugs in crystalline form, and drug-related paraphernalia. Beautifully rendered four-color illustrations present data from important experiments and portray models of drug action, including neural pathways thought to mediate the psychological and behavioral effects of specific substances. Bulleted interim summaries highlight the key points made in each part of the chapter, and study questions are provided at the end of each chapter to assist students in reviewing the most important material. A new feature for this edition is the inclusion of learning objectives at the beginning of each section to help direct students and instructors towards the main content to be covered. Breakout boxes (printed and on the web) categorized by the themes of Pharmacology in Action, The Cutting Edge, Of Special Interest, Clinical Applications, Case Studies, and History of Psychopharmacology highlight topics of particular importance. Finally, the new Enhanced e-book offers access to Web Boxes, study resources such as self assessment at the end of each section, flashcards, weblinks and animations that visually illustrate key neurophysiological and neurochemical processes important for Psychopharmacology.

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Readers familiar with previous editions of this textbook may notice that the long-standing co-author Linda Quenzer was not involved in preparing this new edition. Although Linda has retired from textbook writing, she has been ably replaced by new co-authors Andrew Farrar and Dominik Biezonski. We are confident that this new team, which includes previous contributor Jennifer Yates, has produced a worthy successor to previous editions of the textbook. We hope that you, the reader, will ultimately agree with that assessment.

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Lastly, we would like to acknowledge and thank the many adopters of this textbook and their students. To new adopters, we appreciate your selection and trust that you will still be happy with that selection after having used the book in your classroom. If you are a previous adopter, we thank you for your continued loyalty that has made it possible to reach this Fourth Edition of the book. Finally, if you are a student, we hope that reading our book and studying the field of psychopharmacology might inspire you to choose this exciting and dynamic field for your own career so that in the years to come, your name might be among the researchers cited in a future edition of *Psychopharmacology: Drugs, the Brain, and Behavior.*

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1 Principles of Pharmacology

WILLIAM S. BAER (1872–1931) WAS AN ORTHOPEDIC SURGEON at Johns Hopkins University, where he established the orthopedic department and led it for most of his life, training many of the outstanding orthopedists of the day. During World War I Baer observed that soldiers who had severe and deep flesh wounds did not have the fever associated with infection and showed little of the expected necrotic (dead) tissue damage if there was a significant presence of maggots (fly larvae) in the wounds. Although it had been believed that early peoples (Australian aborigines and Mayan Indian tribes) and others throughout history had used maggots to clean wounds, it was Baer who once again recognized their importance, especially in tense battlefield conditions where infection was especially hard to treat. Apparently the maggots ingested the dying tissue but left healthy tissue intact. Baer, upon doing further "pharmacological" experiments, showed that his hospitalized patients with severe and chronic bone infections showed remarkable recovery after being treated with maggots—the inflamed and dying tissue was ingested, leaving wounds clean and healthy, and new tissue formed. As long as the maggots were sterilized, secondary infections were avoided. After his research, "maggot therapy" became popular and was used throughout the 1930s and 1940s until penicillin was established as an easier treatment for infection. However, it has been suggested that in modern times, maggot therapy will be reintroduced to treat those wounds infected with antibiotic-resistant bacteria. At present in the European Union, Japan, and Canada, maggots are considered "medicinal drugs," and in 2005 the U.S. Food and Drug Administration approved the use of maggots as a medical "device."

What actually causes the amazing healing process is not entirely clear, but pharmacologists are beginning to understand that maggot secretions suppress the immune system and reduce inflammation, and they may also enhance cell growth and increase oxygen concentration in the wound. This is certainly not the first time pharmacology has returned to earlier forms of therapeutics, but the science now can isolate and identify those components that lead to healing. ■

Maggot therapy can be used to clean wounds and prevent infection.

1.1 Pharmacology: The Science of Drug Action

Pharmacology is the scientific study of the actions of drugs and their effects on a living organism. Until the beginning of the last century, pharmacologists studied drugs that were almost all naturally occurring substances. The importance of plants in the lives of ancient humans is well documented. Writings from as early as 1500 BCE describe plant-based medicines used in Egypt and in India. The Ebers Papyrus describes the preparation and use of more than 700 remedies for ailments as varied as crocodile bites, baldness, constipation, headache, and heart disease. Of course, many of these treatments included elements of magic and incantation, but there are also references to some modern drugs such as castor oil and opium. The Chinese also have a very long and extensive tradition in the use of herbal remedies that continues today. World Health Organization estimates suggest that in modern times, as many as 80% of the people in developing countries are totally dependent on herbs or plant-derived medicinals. And in 1999, in the United States, modern herbal medicines and drugs based on natural products represented half of the top 20 drugs on the market (Hollinger, 2008). Many Americans are enamored with herbal medications despite limited clinical support for their effectiveness, because they believe these treatments are more "natural." Nevertheless, serious dangers have been associated with some of them. **WEB BOX 1.1** discusses the benefits and dangers of herbal remedies.

When placed in historical context, it can be seen that drug development in the United States is in its infancy. The rapid introduction of many new drugs by the pharmaceutical industry has forced the development of several specialized areas of pharmacology. Two of these areas are of particular interest to us. **Neuropharmacology** is concerned with drug-induced changes in the functioning of cells in the nervous system, and **psychopharmacology** emphasizes drug-induced changes in mood, thinking, and behavior. In combination, the goal of **neuropsychopharmacology** is to identify chemical substances that act on the nervous system to alter behavior that is disturbed because of injury, disease, or environmental factors. Additionally, neuropsychopharmacologists are interested in using chemical agents as probes to gain an understanding of the neurobiology of behavior.

When we speak of **drug action**, we are referring to the specific molecular changes produced by a drug when it binds to a particular target site or receptor. These molecular changes lead to more widespread alterations in physiological or psychological functions, which we consider **drug effects**. The site of drug action may be very different from the site of drug effect. For example, atropine is a drug used in ophthalmology to dilate the pupil of the eye before eye examinations. Atropine has a site of action (the eye muscles of the iris) that is close to the site of its ultimate effect (widening the pupil), so it is administered directly to the eye. In comparison, morphine applied to the eye itself has no effect. Yet when it is taken internally, the drug's action on the brain leads to "pinpoint" pupils. Clearly, for morphine, the site of effect is far distant from the site of its initial action.

Keep in mind that because drugs act at a variety of target sites, they always have multiple effects. Some may be **therapeutic effects**, meaning that the drug–receptor interaction produces desired physical or behavioral changes. All other effects produced are referred to as **side effects**, and they vary in severity from mildly annoying to distressing and dangerous. For example, amphetamine-like drugs produce alertness and insomnia, increased heart rate, and decreased appetite. Drugs in this class reduce the occurrence of spontaneous sleep episodes characteristic of the disorder called *narcolepsy*, but they produce anorexia (loss of appetite) as the primary side effect. In contrast, the same drug may be used as a prescription diet control in weight-reduction programs. In such cases, insomnia and hyperactivity are frequently disturbing side effects. Thus therapeutic and side effects can change, depending on the desired outcome.

It is important to keep in mind that there are no "good" or "bad" drugs, because all drugs are just chemicals. It is the way a drug is procured and used that determines its character. Society tends to think of "good" drugs as those purchased at a pharmacy and taken at the appropriate dosage for a particular medicinal purpose, and "bad" drugs as those acquired in an illicit fashion and taken recreationally to achieve a desired psychological state. Even with this categorization, the differences are blurred because many people consider alcohol to be "bad" even though it is purchased legally. Morphine and cocaine have legitimate medicinal uses, making them "good" drugs under some conditions, although they can, when misused, lead to dangerous consequences and addiction, making the same drugs "bad." Finally, many "good" prescription drugs are acquired illicitly or are misused by increasing the dose, prolonging use, or sharing the drug with other individuals, leading to "bad" outcomes. As you will read in later chapters, the ideas of Americans about appropriate drug use have changed dramatically over time (see the sections on the history of the use of narcotics in Chapter 11 and cocaine in Chapter 12).

Many of the drug effects we have described so far have been **specific drug effects**, defined as those based on the physical and biochemical interactions of a drug with a target site in living tissue. In contrast, **nonspecific drug effects** are those that are based not on the chemical activity of a drug–receptor interaction, but on certain unique characteristics of the individual. It is clear that an individual's background (e.g., drug-taking

experience), present mood, expectations of drug effect, perceptions of the drug-taking situation, attitude toward the person administering the drug, and other factors influence the outcome of drug use. Nonspecific drug effects help to explain why the same individual self-administering the same amount of ethyl alcohol may experience a sense of being lighthearted and gregarious on one occasion, and depressed and melancholy on another. The basis for such a phenomenon may well be the varied neurochemical states existing within the individual at different times, with which specific drug effects interact.

Placebo effect

Common examples of nonspecific effects are the multiple outcomes that result from taking a **placebo**. Many of you automatically think of a placebo as a "fake" pill. A placebo *is* in fact a pharmacologically inert compound administered to an individual; however, in many instances it has not only therapeutic effects, but side effects as well. Just as many of the symptoms of illness may have psychogenic or emotional origins, belief in a drug may produce real physiological effects despite the lack of chemical activity. These effects are not limited to the individual's subjective evaluation of relief but include measurable physiological changes such as altered gastric acid secretion, blood vessel dilation, hormonal changes, and so forth.

In a classic study, two groups of patients with ulcers were given a placebo. In the first group, the medication was provided by a physician, who assured the patients that the drug would provide relief. The second group also received the placebo, but it was administered by a nurse, who described it as experimental in nature. In group 1, 70% of the patients found significant relief, but in group 2, only 25% were helped by the "drug" (Levine, 1973). Based on these results, it is clear that a sugar pill is not a drug that can heal ulcers, but rather its effectiveness depends on the ritual of the therapeutic treatment that can have both neurobiological and behavioral effects that influence the outcome. It is a perfect example of mind–body interaction, and there has been increasing interest in understanding the mechanism responsible for the placebo effect as a means to enhance the therapeutic effectiveness of drug treatments. Although some consider deliberate prescription of placebos to patients unethical because of the deception involved, other physicians and ethicists have identified appropriate uses for placebos that represent an inexpensive treatment that avoids unnecessary medications.

Placebo effects may in part be explained by Pavlovian conditioning in which symptom improvement in the past has been associated with particular characteristics of a medication, for example its taste, color, shape, and size; a particular recommending clinician, with her white coat, reassuring tone of voice, or attitude; or aspects of the medical facility. Since a placebo effect has been demonstrated many times in animal models, cues in the environment are apparently sufficient, and verbal reassurances are not necessary. In fact, patients have been shown to benefit even if they are told that the medication is a placebo, so deception is apparently not a necessity; however, verbal suggestion interacts with conditioning (see Colagiuri et al., 2015).

A second possible explanation for the placebo effect is that of conscious, explicit expectation of outcomes. For example, those individuals who anticipate relief may show an enhanced placebo response. Of great interest are the placebo-induced neurobiological effects within the brain. Research has shown that when placebos effectively reduce pain, those individuals who are responders have significantly higher levels of natural pain-relieving opioid neuropeptides in their cerebrospinal fluid than those individuals who do not show a response to the placebo. Further, the subjects who anticipate pain relief show reduced neural activity in pain-related brain regions (see Benedetti et al., 2011).

While Pavlovian conditioning and conscious expectation both contribute to the placebo effect, other factors may also have a part (see Murray and Stoessl, 2013; Carlino et al., 2016). Placebo effects may involve social learning. That is, observing another individual anticipating a positive outcome can be a more powerful inducer of the placebo effect than direct conditioning or verbal suggestions. Others have found that anticipating a successful outcome reduces anxiety and activates reward networks in the brain. Finally, a number of genetic variants have been found that influence the placebo effect. Understanding more about which genes identify patients who will respond to placebo could allow treatment to be adjusted to maximize outcome (Colagiuri et al., 2015). This is one step toward personalized medicine (see the last section of this chapter).

In contrast to placebos, negative expectations may increase the level of anxiety experienced, which may also influence the outcome of treatment. Expecting treatment failure when an inert substance is given along with verbal suggestions of negative outcome, such as increased pain or another aversive event, would increase anxiety as well as cause an accompanying change in neural mechanisms, including increases in stress hormones. This is the **nocebo** effect, and both the nocebo-induced increase in pain reported and the hormonal stress response can be reduced by treatment with an antianxiety drug, demonstrating that expectation-induced anxiety plays a part in the nocebo effect. Nocebos are important to study because warnings about potential side effects can lead to greater side-effect occurrence. Unfortunately, because drug companies are required by law to provide a comprehensive listing of all possible side effects, many individuals have negative expectations, leading to increased side effects.

BOX 1.1 ■ PHARMACOLOGY IN ACTION

Naming Drugs

Drug names can be a confusing issue for many people because drugs that are sold commercially, by prescription or over the counter, usually have four or more different kinds of names.

All drugs have a *chemical name* that is a complete chemical description suitable for synthesizing by an organic chemist. Chemical names are rather clumsy and are rarely used except in a laboratory setting. In contrast, *generic* or *nonproprietary names* are official names of drugs that are listed in the United States Pharmacopeia. The generic name is a much shorter form of the chemical name but is still unique to that drug. For example, one popular antianxiety drug has the chemical name 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one and the generic name diazepam. The *brand name*, or *trade name*, of that drug (Valium) specifies a particular manufacturer and a formulation. A brand name is trademarked and copyrighted by an individual company, which means that the company has an exclusive right to advertise and sell that drug.

Slang or *street names* of commonly abused drugs are another way to identify a particular chemical. Unfortunately, these names change over time and vary with geographical location and particular groups of people. In addition, there is no way to know the chemical characteristics of the substance in question. Some terms are used in popular films or television and become more generally familiar, such as "crack" or "ice," but most disappear as quickly as they appear.

In pharmacology, the placebo is essential in the design of experiments conducted to evaluate the effectiveness of new medications, because it eliminates the influence of expectation on the part of the experiment's participants. The control group is identical to the experimental group in all ways and is unaware of the substitution of an inactive substance (e.g., sugar pill, saline injection) for the test medication. Comparison of the two groups provides information on the effectiveness of the drug beyond the expectations of the participants. Of course, drugs with strong subjective effects or prominent side effects make placebo testing more challenging because the experimental group will be aware of the effects while those experiencing no effects will conclude they are the control group. To avoid that problem, some researchers may use an "active" placebo, which is a drug (unrelated to the drug being tested) that produces some side effects that suggest to the control participants that they are getting the active agent. In other cases clinical researchers may feel that it is unethical to leave the placebo group untreated if there is an effective agent available. In that case the control group will be given the older drug, and effectiveness of the new drug will be compared with it rather than with a placebo.

The large contribution of nonspecific factors and the high and variable incidence of placebo responders make the **double-blind experiment** highly desirable. In these experiments, neither the patient nor the observer knows what treatment the participant has received. Such precautions ensure that the results of any given treatment will not be biased on the part of the participant or the observer. If you would like to read more about the use of placebos in both clinical research and therapeutics and the associated ethical dilemmas, refer to the articles by Brown (1998) and Louhiala (2009).

Throughout this chapter, we present examples that include both therapeutic and recreational drugs that affect mood and behavior. Since there are usually several names for the same substance, it may be helpful for you to understand how drugs are named (**BOX 1.1**).

Pharmacokinetic factors determining drug action

Although it is safe to assume that the chemical structure of a drug determines its action, it quickly becomes clear that additional factors are also powerful contributors. The dose of the drug administered is clearly important, but more important is the amount of drug in the blood that is free to bind at specific target sites (**bioavailability**) to elicit drug action. The following sections of this chapter describe in detail the dynamic factors that contribute to bioavailability. Collectively, these factors constitute the **pharmacokinetic** component of drug action; they are listed below and illustrated in **FIGURE 1.1**.

1. *Routes of administration*. How and where a drug is administered determines how quickly and how completely the drug is absorbed into the blood.
2. *Absorption and distribution*. Because a drug rarely acts where it initially contacts the body, it must pass through a variety of cell membranes and enter the blood plasma, which transports the drug to virtually all of the cells in the body.
3. *Binding*. Once in the blood plasma, some drug molecules move to tissues to bind to active target sites (receptors). While in the blood, a drug may

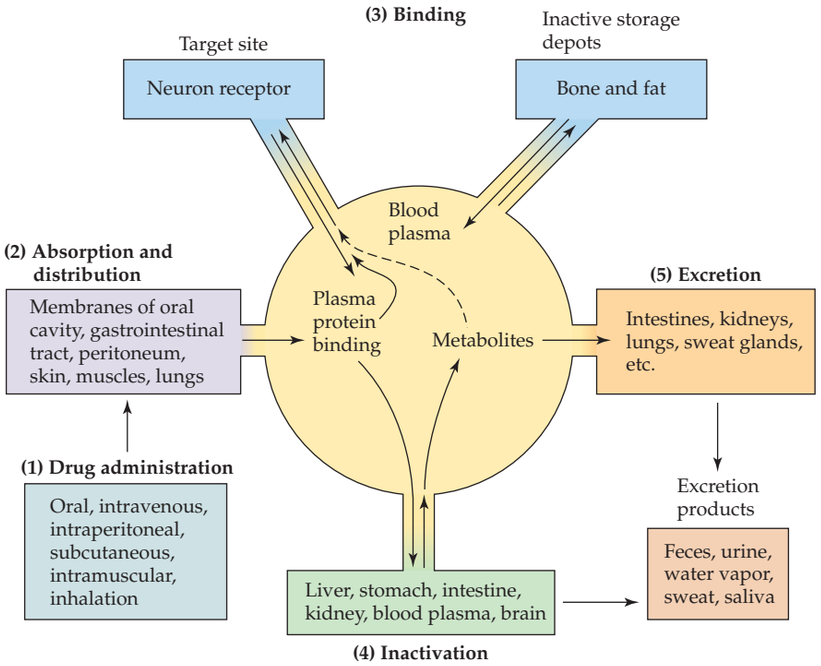

FIGURE 1.1 Pharmacokinetic factors that determine bioavailability of drugs From the site of administration (1), the drug moves through cell membranes to be absorbed into the blood (2), where it circulates to all cells in the body. Some of the drug molecules may bind to inactive sites such as plasma proteins or storage depots (3), and others may bind to receptors in target tissue. Bloodborne drug molecules also enter the liver (4), where they may be transformed into metabolites and travel to the kidneys and other discharge sites for ultimate excretion (5) from the body.

also bind (**depot binding**) to plasma proteins or may be stored temporarily in bone or fat, where it is inactive.

4. *Inactivation*. Drug inactivation, or **biotransformation**, occurs primarily as a result of metabolic processes in the liver as well as other organs and tissues. The amount of drug in the body at any one time is dependent on the dynamic balance between absorption and inactivation. Therefore, inactivation influences both the intensity and the duration of drug effects.
5. *Excretion*. The drug metabolites are eliminated from the body with the urine or feces. Some drugs are excreted in an unaltered form by the kidneys.

Although these topics are discussed sequentially in the following pages, keep in mind that in the living organism, these factors are at work simultaneously. In addition to bioavailability, the drug effect experienced will also depend on how rapidly the drug reaches its target, the frequency and history of prior drug use (see the discussion on tolerance later in the chapter), and nonspecific factors that are characteristics of individuals and their environments.

Methods of drug administration influence the onset of drug action

The route of administration of a drug determines how much drug reaches its site of action and how quickly the drug effect occurs. There are two major categories of administration methods. **Systemic** routes of administration refer to methods in which drugs distribute throughout the entire body, thus reaching the target tissue through general circulation. Within the broad category of systemic administration, **enteral** methods of administration use the gastrointestinal (GI) tract (*enteron* is the Greek word for "gut"); agents administered by these methods are generally slow in onset and produce highly variable blood levels of drug. The most common enteral method of administration is oral, but rectal administration with the use of suppositories is another enteral route. Other systemic routes of administration are **parenteral** and include those that do not use the alimentary canal, such as injection or pulmonary administration.

Oral administration (**PO**) is the most commonly used route for taking drugs, because it is safe, self-administered, and economical, and it avoids the complications and discomfort of injection methods. Drugs that are taken orally come in the form of capsules, pills, tablets, or liquid, but to be effective, the drug must dissolve in stomach fluids and pass through the stomach or intestine wall to reach blood capillaries. In addition, the drug must be resistant to destruction by stomach acid and stomach enzymes that are important for normal digestion.

Movement of the drug from the site of administration to the blood circulation is called **absorption**. Although some drugs are absorbed from the stomach, most drugs are not fully absorbed until they reach the small intestine. Many factors influence how quickly the stomach empties its contents into the small intestine and hence determine the ultimate rate of absorption. For example, food in the stomach, particularly if it is fatty, slows the movement of the drug into the intestine, thereby delaying absorption into the blood. The amount of food consumed, the level of physical activity of the individual, and many other factors

make it difficult to predict how quickly the drug will reach the intestine. In addition, many drugs undergo extensive first-pass metabolism. **First-pass metabolism** is an evolutionarily beneficial function because potentially harmful chemicals and toxins that are ingested pass via the portal vein to the liver, where they are chemically altered by a variety of enzymes before passing to the heart for circulation throughout the body (**FIGURE 1.2**). Unfortunately, some therapeutic drugs taken orally may undergo extensive metabolism (more than 90%), reducing their bioavailability. Drugs that show extensive first-pass effects must be administered at higher doses or in an alternative manner, such as by injection. Because of these many factors, oral administration produces drug plasma levels that are more irregular and unpredictable and rise more slowly than those produced by other methods of administration.

Rectal administration requires the placement of a drug-filled suppository in the rectum, where the suppository coating gradually melts or dissolves, releasing the drug, which will be absorbed into the blood. Depending on the placement of the suppository, the drug may avoid some first-pass metabolism. Drug absorbed from the lower rectum into the hemorrhoidal vein bypasses the liver. However, deeper placement means that the drug is absorbed by veins that drain into the portal vein, going to the liver before the general circulation. Bioavailability of drugs administered in this way is difficult to predict, because absorption is irregular (**BOX 1.2**). Although rectal administration is not used as commonly as oral administration, it is an effective

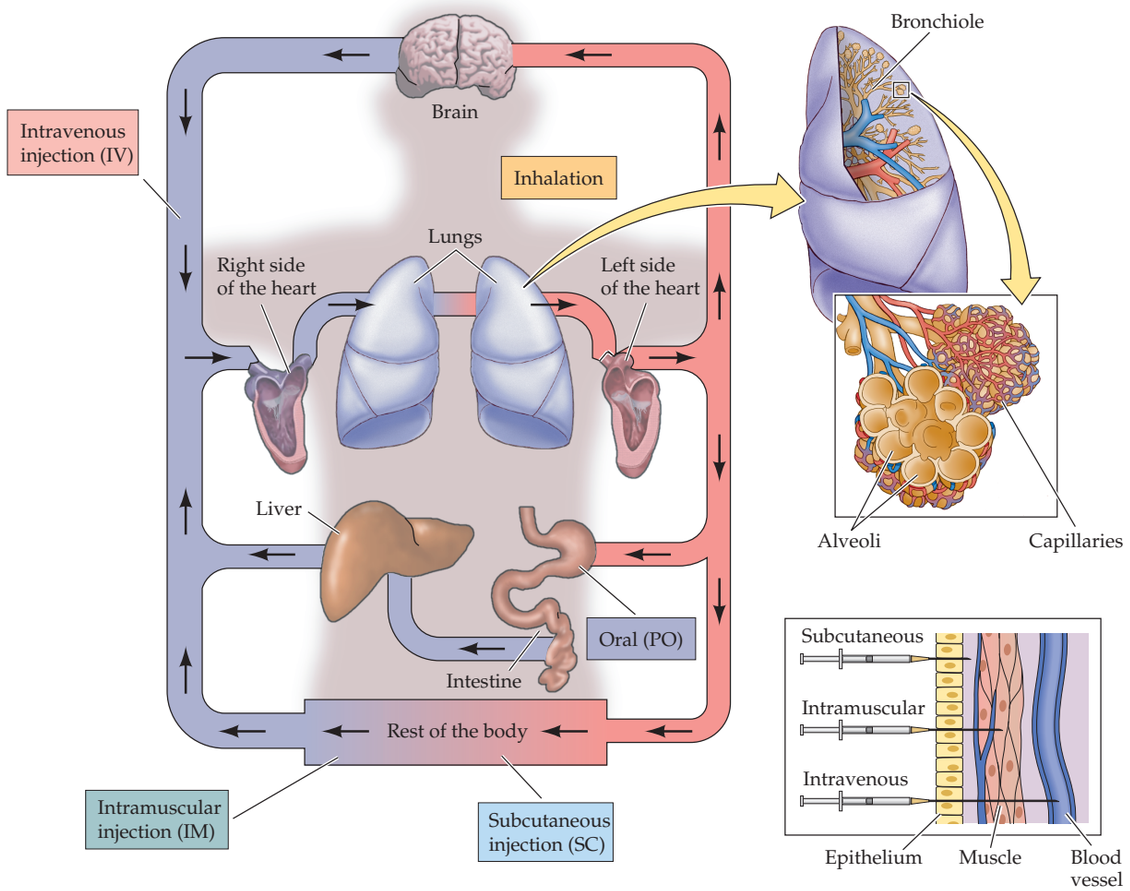

FIGURE 1.2 **Routes of drug administration** First-pass effect. Drugs administered orally are absorbed into the blood and must pass through the liver before reaching the general circulation. Some drug molecules may be destroyed in the liver before they can reach target tissues. The arrows indicate the direction of blood flow in the arteries (red) and veins (blue). (Top inset) Pulmonary absorption through capillaries in the alveoli. Rapid absorption occurs after inhalation because the large surface area of the lungs and the rich capillary networks provide efficient exchange of gases to and from the blood. (Bottom inset) Methods of administration by injection. The speed of absorption of drug molecules from administration sites depends on the amount of blood circulating to that area.

route in infants and in individuals who are vomiting, unconscious, or unable to take medication orally.

Intravenous (**IV**) injection is the most rapid and accurate method of drug administration in that a precise quantity of the agent is placed directly into the blood and passage through barriers such as the stomach wall is eliminated (see Figure 1.2). However, the quick onset of drug effect with IV injection is also a potential hazard. An overdose or a dangerous allergic reaction to the drug leaves little time for corrective measures, and the drug cannot be removed from the body as it can be removed from the stomach by stomach pumping.

For drug abusers, IV administration provides a more dramatic subjective drug experience than self-administration in other ways, because the drug reaches the brain almost instantly. Drug users report that intravenous injection of a cocaine solution usually produces an intense "rush" or "flash" of pure pleasure that lasts for approximately 10 minutes. This experience rarely occurs when cocaine is taken orally or is taken into the nostrils (snorting; see the discussion on topical administration). However, IV use of street drugs poses several special hazards. First, drugs that are impure or of unknown quality provide uncertain doses, and toxic reactions are common. Second, lack of sterile injection equipment and aseptic technique can lead to infections such as hepatitis, human immunodeficiency virus (HIV), and endocarditis (inflammation of the lining of the heart). Fortunately, many cities have implemented free needle programs, which significantly reduce the

BOX 1.2 ■ CASE STUDIES

The Perils of Alcohol Taken by an Unconventional Route of Administration

As described in this chapter, pharmacokinetic factors play a significant role in drug bioavailability and hence drug effects. With respect to drugs of abuse, many drug users experiment with alternative routes of administration in order to avoid unpleasant side effects or enhance the desired effects of a given drug. Ethyl alcohol, or ethanol, is consumed almost exclusively orally, in the form of a fermented drink, like beer or wine, or as a distilled spirit, like vodka or whiskey. When consumed by the oral route of administration, ethanol has relatively high bioavailability. However, because most ethanol is absorbed in the intestines, the stomach contents, and thus the rate of gastric emptying, can powerfully influence ethanol absorption and bioavailability.

Even though nearly all ethanol is consumed orally, even in cases of excessive consumption and abuse, some individuals have engaged in the dangerous practice of administering ethanol-containing drinks rectally, as an alcohol enema. The practice of rectally administering alcohol is highly risky for a couple of notable reasons. Alcohol, particularly at higher concentrations, is highly irritating to the sensitive mucosa of the colon, and as such, exposure to alcohol-containing drinks has resulted in numerous cases of severe colitis, requiring hospitalization. More seriously, the colon absorbs alcohol very rapidly, and unlike the stomach, the colon does not contain alcohol dehydrogenase (ADH), which normally begins the biotransformation of ethanol in the stomach before it is absorbed into the bloodstream. Moreover, ethanol absorbed through the colon does not undergo first-pass metabolism, further contributing to its elevated bioavailability. The more rapid absorption and hence higher bioavailability of ethanol through rectal administration can result in a blood-alcohol concentration that is significantly higher than if the same amount of ethanol were consumed orally. The higher bioavailability and thus more pronounced intoxicating effect of alcohol is likely chief among the reasons that some individuals choose to administer alcohol rectally. Other reasons may include avoidance of vomiting as well as the false belief that rectally administered alcohol would be undetectable on the breath.

Peterson and colleagues (2014) present the case of a 52-year-old man who was found deceased in his home following rectal administration of wine. At the time of autopsy, the decedent's blood-alcohol concentration was 350 mg/dL, while the vitreous ethanol concentration was 410 mg/dL. Determining postmortem alcohol content from the vitreous fluid of the eye is thought to reflect alcohol concentration more accurately at the time of death, since blood levels of alcohol tend to vary quite widely and decrease in the postmortem period. In any event, it is likely that the blood-alcohol concentration in the decedent was at least in the range of 350 to 410 mg/dL at the time of death, which is well within the range at which most people would suffer the fatal effects of ethanol.

While accidental ethanol overdoses resulting in death are relatively common, it is unusual that these fatal overdoses are the result of rectal administration. Given the high bioavailability of ethanol from this route of administration and hence the elevated potential for unintentional overdose, the small number of fatal overdoses likely reflects the fact that while dangerous, alcohol enema is a far less commonly used method of administration than oral consumption. As discussed in Chapter 10, alcohol overdose by any route of administration represents a fraction of the total number of alcohol-related fatalities, which can include fatalities caused by other dangerous behaviors, including motor vehicle accidents.

probability of cross-infection. Third, many drug abusers attempt to dissolve drugs that have insoluble filler materials, which, when injected, may become trapped in the small blood vessels in the lungs, leading to reduced respiratory capacity or death.

An alternative to the IV procedure is **intramuscular** (**IM**) injection, which provides the advantage of slower, more even absorption over a period of time. Drugs administered by this method are usually absorbed within 10 to 30 minutes. Absorption can be slowed down by combining the drug with a second drug that constricts blood vessels, because the rate of drug absorption is dependent on the rate of blood flow to the muscle (see Figure 1.2). To provide slower, sustained action, the drug may be injected as a suspension in vegetable oil. For example, IM injection of medroxyprogesterone acetate (Depo-Provera) provides effective contraception for 3 to 6 months without the need to take daily pills. One disadvantage of IM administration is that in some cases, the injection solution can be highly irritating, causing significant muscle discomfort.

Intraperitoneal (**IP**) injection is rarely used with humans, but it is the most common route of administration for small laboratory animals. The drug is injected through the abdominal wall into the peritoneal cavity—the space that surrounds the abdominal organs. IP injection produces rapid effects, but not as rapid as those produced by IV injection. Variability in absorption occurs, depending on where (within the peritoneum) the drug is placed.

In **subcutaneous** (**SC**) administration, the drug is injected just below the skin (see Figure 1.2) and is absorbed at a rate that is dependent on blood flow to the site. Absorption is usually fairly slow and steady, but there can be considerable variability. Rubbing the skin to dilate blood vessels in the immediate area increases the rate of absorption. Injection of a drug in a nonaqueous solution (such as peanut oil) or implantation of a drug pellet or delivery device further slows the rate of absorption. Subcutaneous implantation of drug-containing pellets is most often used to administer hormones. Implanon and Nexplanon are two contraceptive implants now available in the United States. The hormones are contained in a single small rod about 40 mm (1.5 inches) long that is implanted through a small incision just under the skin of the upper arm. A woman is protected from pregnancy for a 3-year period unless the device is removed. Recent technological advances allow drug solutions to be injected in a liquid form, which, upon contact with subcutaneous tissue fluid, forms a biodegradable solid or gel that slowly releases active drug over a period of up to 1 month. This technology has been used to administer buprenorphine, which acts as a partial agonist or antagonist at opioid receptors. This mechanism of action is thought to help individuals overcome opioid use disorder by reducing drug withdrawal and promoting treatment compliance due to the long duration of effect (see Ling et al., 2019; Rosenthal, 2019, for detailed reviews of the effectiveness of these novel formulations). Also, refer to Chapter 11 for information about the endogenous opioid system and drugs that act upon it.

Inhalation of drugs, such as those used to treat asthma attacks, allows drugs to be absorbed into the blood by passing through the lungs. Absorption is very rapid because the area of the pulmonary absorbing surfaces is large and rich with capillaries (see Figure 1.2). The effect on the brain is very rapid because blood from the capillaries of the lungs travels only a short distance back to the heart before it is pumped quickly to the brain via the carotid artery, which carries oxygenated blood to the head and neck. The psychoactive effects of inhaled substances can occur within a matter of seconds.

Inhalation is the method preferred for self-administration in cases when oral absorption is too slow and much of the active drug would be destroyed in the GI tract before it reached the brain. Nicotine released from the tobacco of a cigarette by heat into the smoke produces a very rapid rise in blood level and rapid central nervous system (CNS) effects, which peak in a matter of minutes. Tetrahydrocannabinol (THC), an active ingredient of marijuana, and crack cocaine are also rapidly absorbed after smoking. In addition to the inherent dangers of the drugs themselves, disadvantages of inhalation include irritation of the nasal passages and damage to the lungs caused by small particles that may be included in the inhaled material.

Topical application of drugs to mucous membranes, such as the conjunctiva of the eye, the oral cavity, nasopharynx, vagina, colon, and urethra, generally provides local drug effects. Because topically applied drugs are typically intended to act locally, this method of drug administration is generally not considered a systemic route of administration. However, some topically administered drugs can nevertheless be readily absorbed into the general circulation, leading to widespread effects. A related delivery method is **sublingual administration**, which involves placing the drug under the tongue, where it contacts the mucous membrane and is absorbed rapidly into a rich capillary network. Sublingual administration has several advantages over oral administration, because the drug is not broken down by gastric acid or gastric enzymes. Further, its absorption is faster because it is absorbed directly into the blood and is not dependent on those factors that determine how quickly the stomach empties its contents into the small intestine. Additionally, since the drug is not absorbed from the GI tract, it avoids first-pass metabolism. **Intranasal administration** is of special interest because it causes local effects such as relieving nasal congestion and treating allergies, but it can also have systemic effects, in which case the drug

moves very rapidly across a single epithelial cell layer into the bloodstream, avoiding first-pass liver metabolism and producing higher bioavailability than if given orally. The approach is noninvasive, painless, and easy to use, and hence it enhances compliance. Even more important is the fact that intranasal administration allows the blood–brain barrier to be bypassed, perhaps by achieving direct access to the fluid that surrounds the brain (**cerebrospinal fluid** [**CSF**]) and moving from there to extracellular fluid found in the intercellular spaces between neurons. (For a discussion of the potential mechanisms by which intranasal administration can bypass the blood–brain barrier, see Crowe et al., 2018.) A large number of drugs, hormones, steroids, proteins, peptides, and other large molecules are available in nasal spray preparations for intranasal delivery, although not all drugs can be atomized. Hence, neuropeptides such as the hormone oxytocin can be administered by intranasal sprays to achieve significant concentrations in the brain. **WEB BOX 1.2** describes a study that evaluated the effects of intranasal oxytocin administration on social behavior in autistic adults.

Intranasal absorption can also be achieved without dissolving the drug. Direct application of finely powdered cocaine to the nasal mucosa by sniffing leads to rapid absorption, which produces profound effects on the CNS that peak in about 15 to 30 minutes. One side effect of "snorting" cocaine is the formation of perforations in the nasal septum, the cartilage that separates the two nostrils. This damage occurs because cocaine is a potent vasoconstrictor. Reducing blood flow deprives the underlying cartilage of oxygen, leading to necrosis. Additionally, contaminants in the cocaine act as chemical irritants, causing tissue inflammation. Cocaine addicts whose nasal mucosa has been damaged by chronic cocaine "snorting" may resort to application of the drug to the rectum, vagina, or penis.

Although the skin provides an effective barrier to the diffusion of water-soluble drugs, certain lipid-soluble substances (i.e., those that dissolve in fat) are capable of penetrating slowly. Accidental absorption of industrial and agricultural chemicals such as tetraethyl lead, organophosphate insecticides, and carbon tetrachloride through the skin produces toxic effects on the nervous system and on other organ systems. **Transdermal** (i.e., through the skin) drug administration with skin patches provides controlled and sustained delivery of drug at a preprogrammed rate. The method is convenient because the individual does not have to remember to take a pill, and it is painless without the need for injection. It also provides the advantage of avoiding the first-pass effect. In cases of mass vaccination campaigns, transdermal delivery is much quicker than other methods, and it reduces the dangers of accidental needle sticks of health care workers and unsafe disposal of used needles. Conventional patches consist of a polymer matrix embedded with the drug in high concentration. Transdermal delivery is now a common way to prevent motion sickness with scopolamine, reduce cigarette craving with nicotine, relieve angina pectoris with nitroglycerin, and provide hormones after menopause or for contraceptive purposes. The major disadvantage of transdermal delivery is that because skin is designed to prevent materials from entering the body, a limited number of drugs are able to penetrate. However, techniques are continuing to be developed to increase skin permeability through a variety of methods. For instance, handheld ultrasound devices that send low-intensity sound energy waves through surrounding fluid in the tissue temporarily increase the size of the pores in the skin, allowing absorption of large molecules from a skin patch. Other "active" patch systems that help to move large molecules through the skin use iontophoresis, which involves applying a small electrical current with tiny batteries to the reservoir or the patch. The electrical charge repels drug molecules with a similar charge and forces them through the skin at a predetermined rate. If the amount and duration of current are changed, drug delivery can be restricted to the skin for local effects or can be forced more deeply into the blood. This process is also capable of pulling molecules out through the skin for monitoring. Such monitoring might be used by diabetic individuals to more frequently and painlessly evaluate levels of blood glucose. An additional approach uses mechanical disruption of the skin. Small arrays of microneedles about 1 μm in diameter and 100 μm long and coated with drug or vaccine are placed on the skin. The needles penetrate the superficial layer of the skin—the stratum corneum—where the drug is delivered without stimulating underlying pain receptors. This method provides the opportunity for painless vaccinations and drug injections that can be self-administered. These and other developing techniques have been described by Langer (2003), Banga (2009), and Waghule and colleagues (2019).

Special injection methods must be used for some drugs that act on nerve cells, because a cellular barrier, the blood–brain barrier (discussed later in the chapter), prevents or slows passage of these drugs from the blood into neural tissue. To directly bypass the blood–brain barrier, **central** routes of administration may be used. For example, **intrathecal** injection is used when spinal anesthetics are administered directly into the CSF in the subarachnoid space surrounding the spinal cord, whereas **epidural** infusion, in which a catheter is implanted in the epidural space just outside of the dura mater, is commonly used during childbirth, bypassing the blood–brain barrier (**FIGURE 1.3**). In animal experiments, a microsyringe or a cannula enables precise drug infusion into discrete areas of brain tissue (**intracranial**) or into