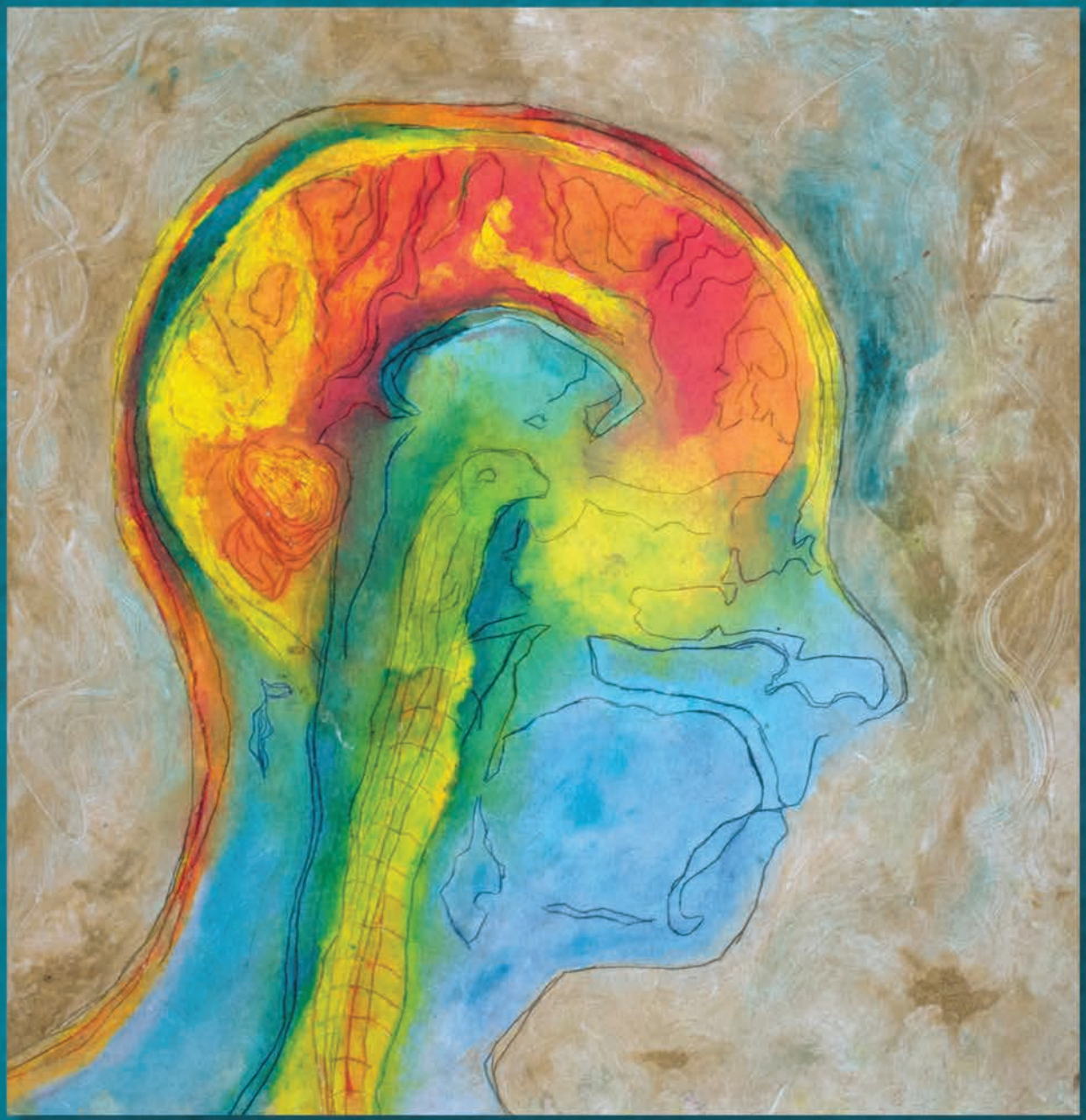
Psychopharmacology

Drugs, the Brain, and Behavior

THIRD EDITION



Jerrold S. Meyer ▪ Linda F. Quenzer

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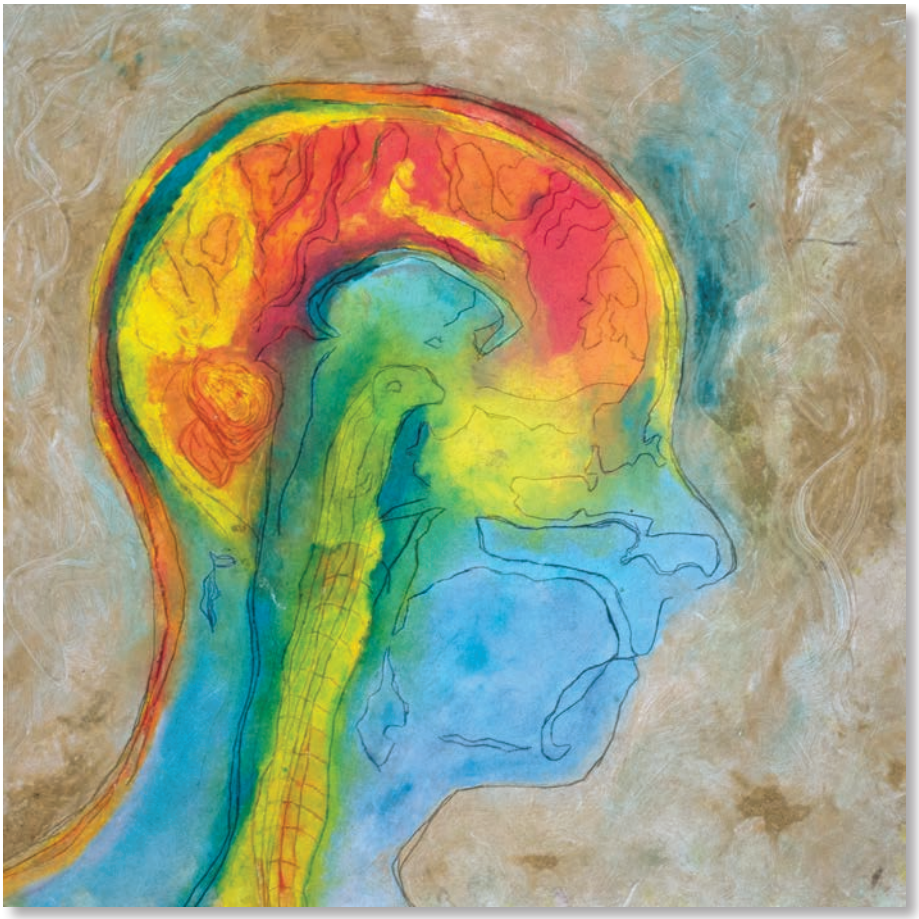

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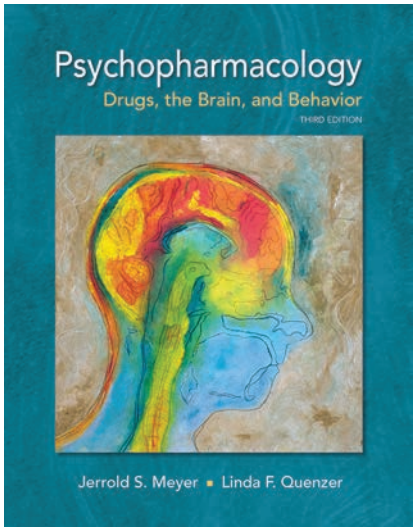

About the cover

"Mind on Fire," portrait of the artist's brain based on saggital MRI. By Elizabeth Jameson. (www.jamesonfineart.com)

Psychopharmacology
Drugs, the Brain, and Behavior, Third Edition

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To our students, who challenge and inspire us,
and to the many outstanding researchers
whose work is central to this book's contents.

Brief Contents

Contents

Preface

When we wrote the preface to the Second Edition of *Psychopharmacology: Drugs, the Brain, and Behavior*, we were struck by the many exciting developments in the field and the remarkable rate of progress elucidating the underlying neurobiological mechanisms of psychoactive drug action. This has not changed over the 5 years since the publication of that edition. The entire field of neuroscience, including neuropsychopharmacology, continues to be driven by technical advances. Using optogenetics, neurobiologists can activate or suppress anatomically and molecularly defined populations of nerve cells with amazing temporal precision. Neuropharmacologists can visualize the 3-dimensional structure of neurotransmitter receptors, enabling synthetic chemists to design novel agonist or antagonist drugs with much greater selectivity than could have been possible before. And huge projects like the Human Connectome Project (www.humanconnectomeproject.org) are using the most advanced neuroimaging techniques to map the detailed circuitry of the living human brain. Because of these technical innovations, we continue to add new information to Chapter 4, on *Methods of Research in Psychopharmacology*. Readers may choose to go through the chapter in its entirety to familiarize themselves with all of the neuropharmacological and behavioral methods reviewed, or they may choose to use the chapter as a reference source when they encounter an unfamiliar method in one of the book's later chapters.

Development and introduction of new pharmaceutical compounds continues as well, although the emphasis has somewhat shifted away from the large pharmaceutical companies to a greater reliance on drug discovery efforts by researchers at universities and medical centers. Statistics show that development of new drugs for CNS disorders (e.g., schizophrenia, depression, and Alzheimer's disease) costs more than for other kinds of disorders, and the failure rate is significantly higher. These data have caused many of the large companies to downsize their CNS drug discovery programs. As you read the chapters on drug addiction, mental disorders, and neurodegenerative disorders, it will become apparent that new medications for these disorders are being introduced at a slower rate than expected, despite ongoing research that continues to identify potential new molecular targets for pharmacotherapy. For this reason, we must admit that exciting advances in understanding the basic structure and function of the nervous system have not yet led to similar progress in treating, much less "curing," disorders of this system. We came to the same conclusion when writing the preface to the Second Edition, so it's disappointing that the hoped-for surge in medication development failed to occur during the intervening period.

As before, this new edition of the text is completely updated to incorporate the latest research findings, methodological advances, and novel drugs of abuse. Regarding the latter, illicit drug labs in the United States and abroad are working hard to turn out massive amounts of recreational drugs, whether already known compounds such as cocaine or fentanyl, or novel synthetic compounds that can only be identified by submitting drug seizures to advanced forensic laboratories for chemical analysis. The national drug epidemic involving fentanyl, heroin, and other opioid compounds is discussed in Chapter 11. New and, in some cases, highly dangerous stimulant and cannabinoid drugs are introduced in Chapters 12, 14, and 15 respectively. Most chapters have new opening vignettes and breakout boxes, and new photographs, drawings, and graphs have been added to bring attention both to updated material and to completely new topic areas for discussion.

Importantly, in preparing this next edition of the book we have maintained our conviction that a deep understanding of the relationship between drugs and behavior requires basic knowledge of how the nervous system works and how different types of drugs interact with nervous system function (i.e., mechanisms of drug action). We have also continued to present the methods and findings from behavioral pharmacological studies using animal models alongside key studies from the human clinical research literature. Pharmacologists must depend on in vitro preparations and laboratory

animal studies for determining mechanisms of drug action, for screening new compounds for potential therapeutic activity, and, of course, for basic toxicology and safety testing. In cases in which clinical trials have already been performed based on promising preclinical results, both sets of findings are presented. In other instances in which clinical trials had not yet been undertaken at the time of our writing, we have striven to point you toward new directions of drug development so that you can seek out the latest information using your own research efforts.

A new point of emphasis in the text concerns neural circuits as mediators of behavior and as targets of drug action. As implied above in referring to the Human Connectome Project, focusing on circuits instead of cells as the nervous system's functional units is the contemporary way to think about how our brains control our actions, and how drugs, whether recreational or medicinal, alter our subjective awareness and behavior.

The Third Edition of *Psychopharmacology: Drugs, the Brain, and Behavior* retains the same four-section organization as the previous editions. Chapters 1 through 4 provide extensive foundation materials, including the basic principles of pharmacology, neurophysiology and neuroanatomy, cell signaling (primarily synaptic transmission), and current methods in behavioral assessment and neuropharmacology. An increased use of clinical examples demonstrates the relevance of the material to real-life issues. Chapters 5 through 8 describe key features of major neurotransmitter systems, including the catecholamines, serotonin, acetylcholine, glutamate, and GABA. These are the neurotransmitter systems most often associated with psychoactive drug effects, and presentation of their neurochemistry, anatomy, and function lays the groundwork for the chapters that follow. Chapters 9 through 16 cover theories and mechanisms of drug addiction and all the major substances of abuse. Finally, Chapters 17 through 20 consider the neurobiology of neuropsychiatric and neurodegenerative disorders and the drugs used to treat these disorders. Among the neuropsychiatric disorders, special emphasis is placed on affective disorders such as major depression and bipolar disorder, various anxiety disorders, and schizophrenia. Bulleted interim summaries highlight the key points made in each part of the chapter. New to this edition, study questions are provided at the end of each chapter to assist students in reviewing the most important material. Finally, a dedicated website for the book (oup-arc.com/access/meyer-3e) is available that offers Web Boxes (advanced topics for interested readers), study resources such as flashcards, web links, and animations that visually illustrate key neurophysiological and neurochemical processes important for psychopharmacology.

It has been our privilege in the first two editions of *Psychopharmacology: Drugs, the Brain, and Behavior* to introduce so many students to the study of drugs and behavior. With this new and updated edition, we hope to continue this tradition and perhaps inspire some of you to continue your studies in graduate school and join the thousands of researchers worldwide who are working to better understand and ultimately defeat illnesses like addiction, depression, schizophrenia, and Alzheimer's disease.

Acknowledgments

This book is the culmination of the efforts of many dedicated people who contributed their ideas and hard work to the project. We'd like to thank and acknowledge the outstanding editorial team at Sinauer Associates: Sydney Carroll, Martha Lorantos, and Danna Lockwood, thank you all for your suggestions for improving the Third Edition, your help and guidance throughout the process of writing and revising, and not least for your patience (textbook writing is a slow process when one is simultaneously teaching, conducting research, and meeting administrative responsibilities). You were unwavering in your vision to produce the best possible psychopharmacology textbook. Mark Siddall did a superb job of seeking out just the right photographs for the book. We are indebted to other key staff members of Sinauer Associates who worked on this project, including Chris Small, Ann Chiara, and Joan Gemme. And we must acknowledge Dragonfly Media Group for the beautiful job rendering the illustrations.

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Psychopharmacology

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CHAPTER 1

Maggot therapy can be used to clean wounds and prevent infection. (PA Images/Alamy Stock Photo.)

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. Presently 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. ■

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, over which specific drug effects are superimposed.

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 interactions with other 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). There have been suggestions that patients might be trained to respond to a placebo by alternating days of placebo treatment with days of active drug treatment. That would allow the reduction of the use of the active agent, potentially minimizing side effects and reducing the cost of treatment.

A second possible explanation for the placebo effect is that of conscious, explicit expectation of outcomes. For example, those individuals who anticipate relief, that is, individuals with an optimistic outlook, 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).

There is every reason to believe that Pavlovian conditioning and conscious expectation both contribute to the placebo effect, but other factors may also have a part (see Carlino et al., 2016; Murray and Stoessl, 2013). 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). A model of these psychosocial–psychobiological factors is shown in **FIGURE 1.1**.

In contrast to placebos, negative expectations may increase the level of anxiety experienced, which may also influence 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 causing an accompanying change in

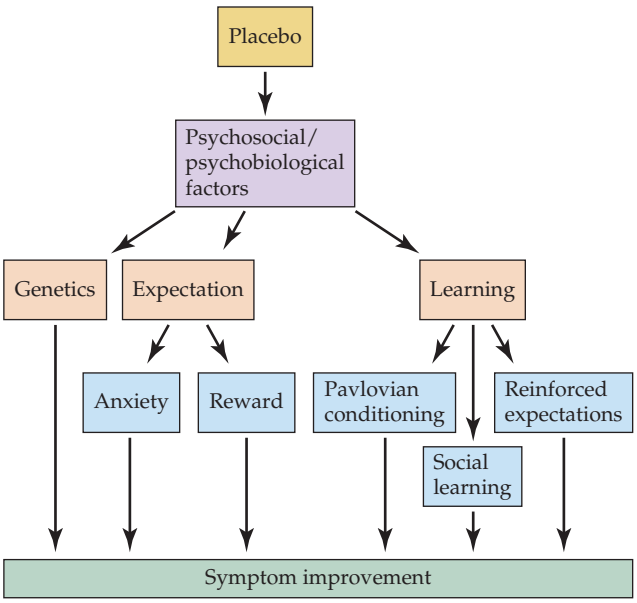

FIGURE 1.1 Placebo effects A model of psychosocial–psychobiological factors that influence clinical improvement following placebo administration. (After Benedetti et al., 2011.)

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.

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

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 names (also called 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 geographic 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. The National Institute on Drug Abuse (NIDA) has compiled a list of more than 150 street names for marijuana and more than 75 for cocaine, including coke, big C, nose candy, snow, mighty white, Foo-foo dust, Peruvian lady, dream, doing the line, and many others.

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 colored by overt or covert prejudices 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 1.2**.

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 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

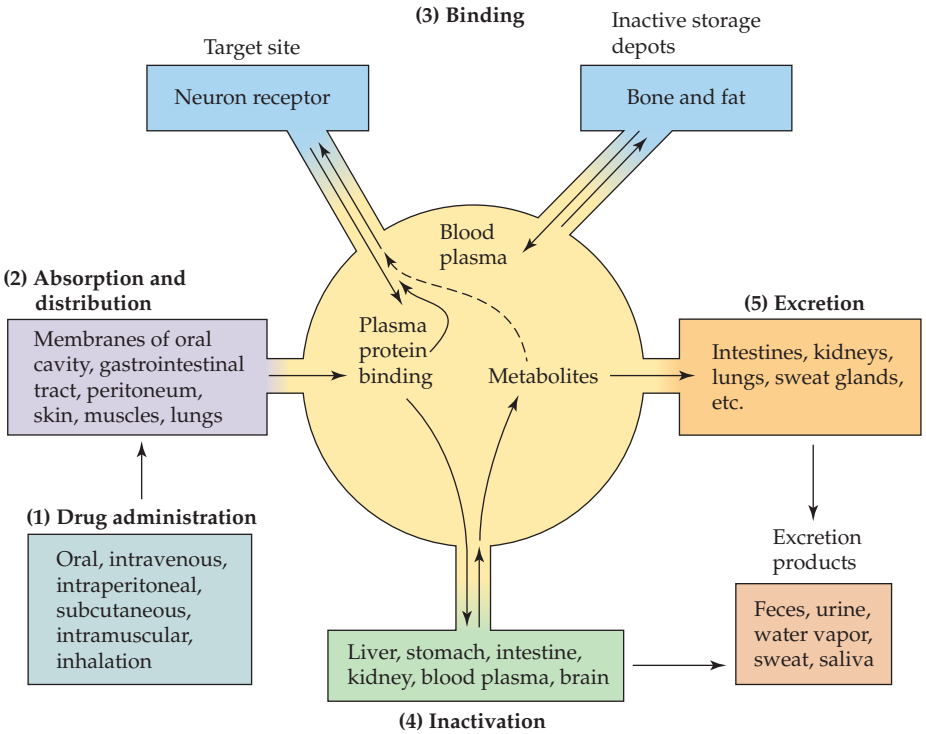

FIGURE 1.2 Pharmacokinetic factors that determine bioavailability of drugs From the site of administration (1), the drug moves through cell membranes to be absorbed into the blood (2), where it circulates to all cells in the body. Some of the drug molecules may bind to inactive sites such as plasma proteins or storage depots (3), and others may bind to receptors in target tissue. Blood-borne 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.

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 liver 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. **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. All other routes of administration are **parenteral** and include those that do not use the alimentary canal, such as injection, pulmonary, and topical administration.

Oral administration (**PO**) is the most popular 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 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. Insulin is one drug that can be destroyed by digestive processes, and for this reason it currently cannot be administered orally. However, several pharmaceutical companies have been actively testing various forms of insulin, believing an oral drug would make insulin therapy for diabetes less complicated and unpleasant and lead to better compliance with the treatment regimen. Although there is no oral insulin, there are some oral medications available that may be effective for some diabetic patients because they inhibit the digestion of starches or increase the amount of glucose excreted in the urine.

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 1.3**). 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. Although rectal administration is not used as commonly as oral administration, it is an effective 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 cell membranes such as the stomach wall is eliminated (see Figure 1.3). 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

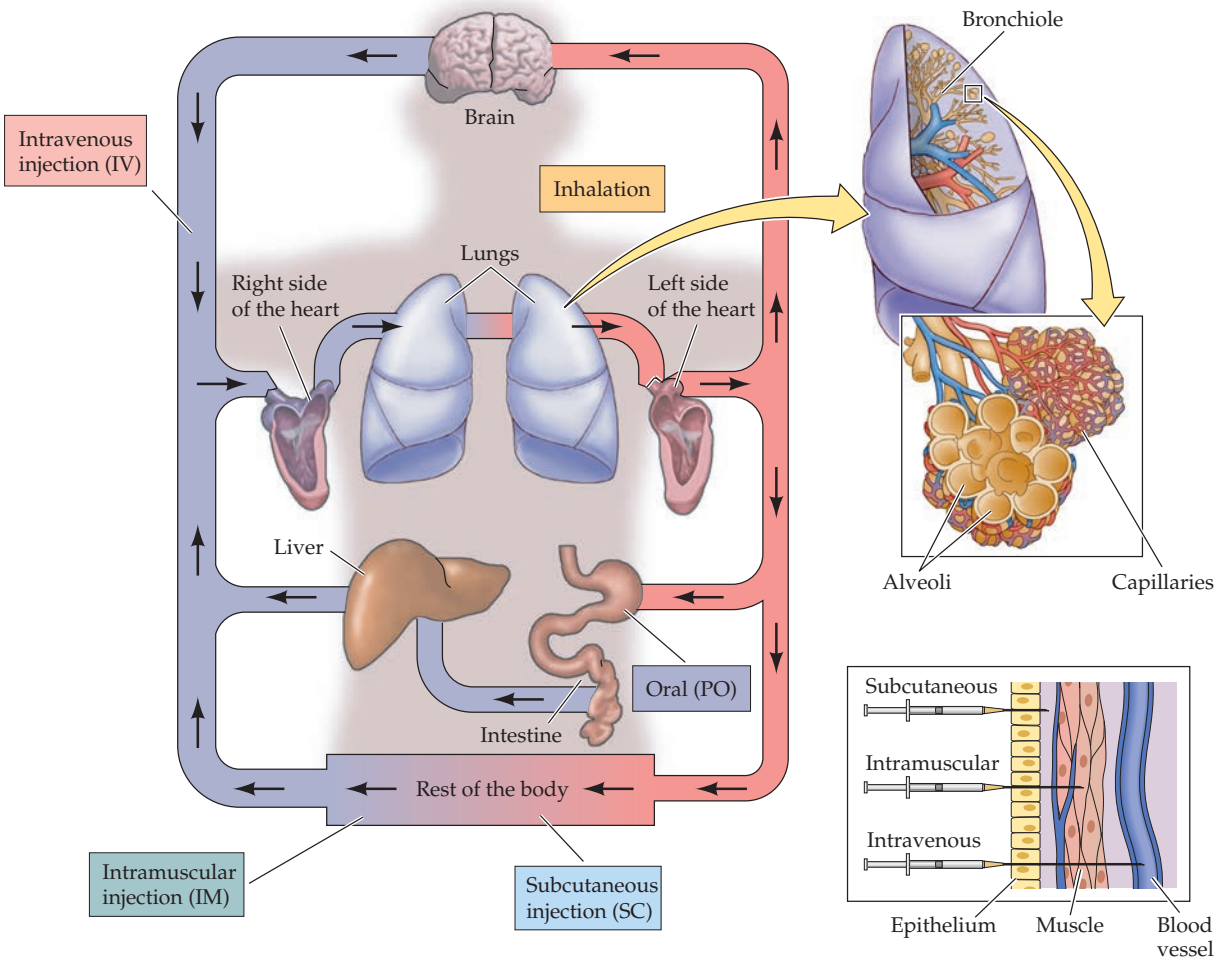

FIGURE 1.3 Routes of drug administration First-pass effect. Drugs administered orally are absorbed into the blood and must pass through the liver before reaching the general circulation. Some drug molecules may be destroyed in the liver before they can reach target tissues. The arrows indicate the direction 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.

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, intravenous 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 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 1.3). To provide slower, sustained action, the