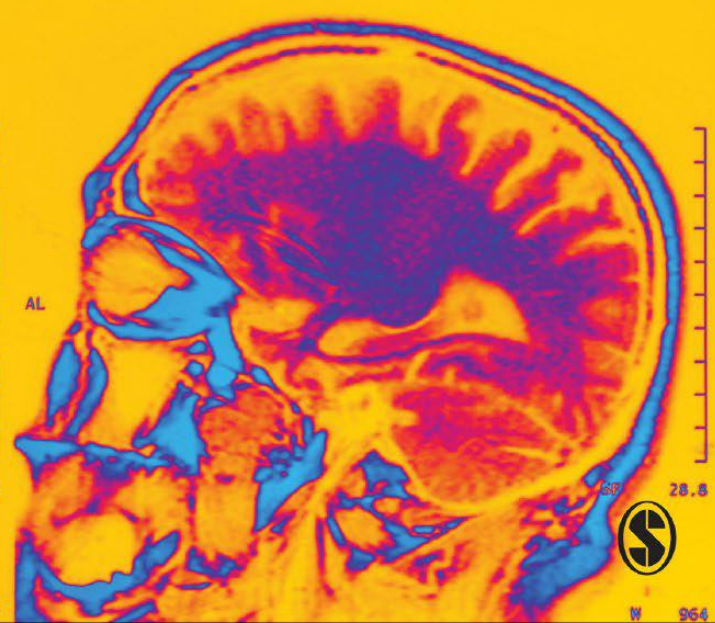
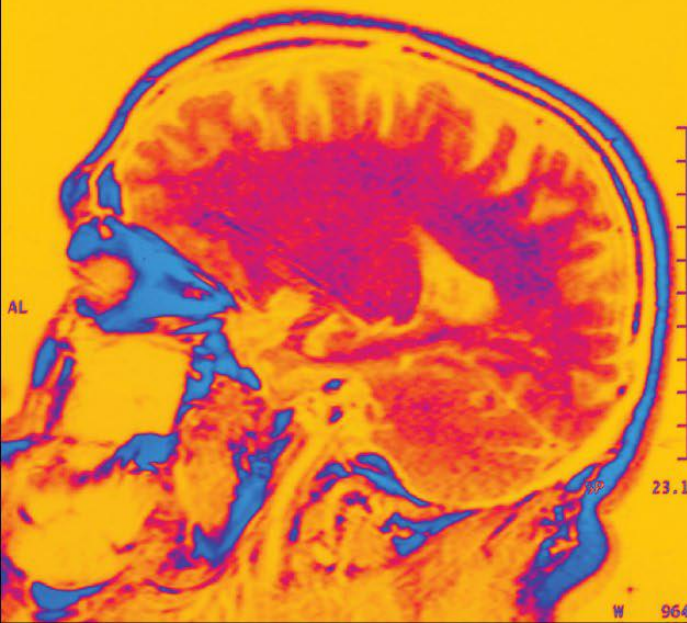
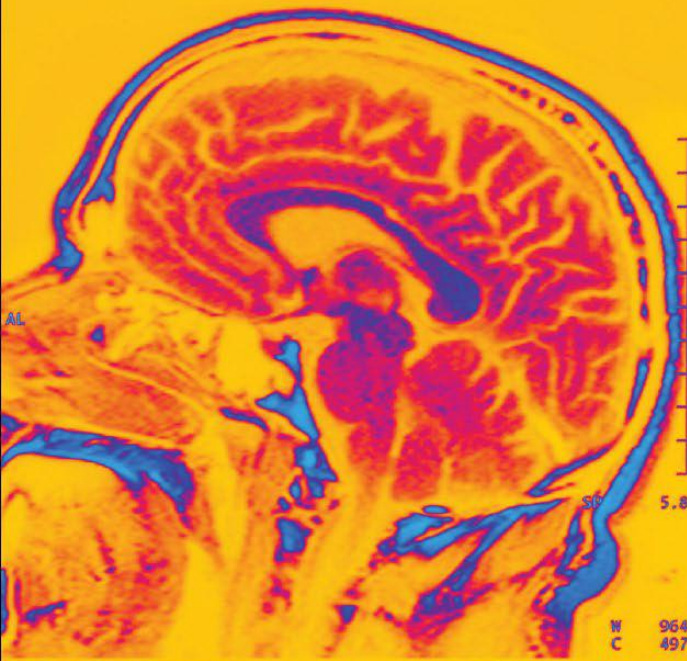


3 EDITION

DRUGS AND THE NEUROSCIENCE OF BEHAVIOR

►► An Introduction to
Psychopharmacology

ADAM PRUS



To my psychopharm students

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Drugs and the Neuroscience of Behavior

An Introduction to Psychopharmacology

Third Edition

Adam Prus

Northern Michigan University



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Preface

D*rugs and the Neuroscience of Behavior: An Introduction to Psychopharmacology*, third edition, provides broad coverage of the fundamental concepts and principles of psychopharmacology. These include how drugs enter and travel through the body, the various actions psychoactive drugs can have in the brain, and the many types of behavioral and physiological effects brought about by the actions of drugs in the brain. These topics are presented early in the book and show how they can help us to understand the use, actions, and effects of different classes of drugs, including psychostimulants, depressants, cannabis, psychedelics, and drugs used for treating mental disorders.

The prior editions of this text came from an emphasis of connecting basic research findings to the effects we find in humans. In doing so, students not only learn how drugs act on the nervous system to produce pharmacological effects, but they also learn about the techniques used to study psychoactive drugs. This is a rapidly advancing field that makes another edition of this book necessary. For example, at the time the second edition was written, nicotine vaping was a new phenomenon and psychedelic drugs for depression were little more than academic theory. At the time of writing the current edition, vaping is common and ketamine is FDA approved for depression.

How the Materials Are Organized

Like the second edition, the third edition provides a number of features that help to facilitate the delivery of this material to students. Information in the book is provided in a careful, step-by-step presentation of information supplemented by illustrations, figures, boxes, and several unique pedagogical features. These features include the following.

From Actions to Effects. Each chapter ends with a section called “From Actions to Effects.” These sections cover a topic that brings together information presented in the chapter, focusing on a concept that requires understanding a drug’s actions to account for its effects. These sections aid in the conceptual understanding of chapter material.

Stop & Check. Stop & Check questions conclude each section in each chapter. These questions allow students to self-assess their understanding of main points covered in the previous section before moving on to the next one.

Review! Chapters include important reminders of facts or concepts covered in previous chapters to help integrate the diverse material covered in this text.

Drug Profiles. This feature provides important basic information about a key compound. Information in these profiles includes a drug's generic name, trade name, and/or street name and provides a description of its pharmacological actions.

Research Techniques and Methods. Chapters include boxes that cover a research technique or method used in psychopharmacology research. These boxes model good working science and provide an easy reference when students come across research findings derived from each technique. These studies are also important in fostering critical thinking habits in students.

Key Terms. Each chapter ends with a list of key terms from the chapter. A definition is provided for each key term in a glossary at the end of the book.

Changes in the Third Edition

This third edition of *Drugs and the Neuroscience of Behavior: An Introduction to Psychopharmacology* contains major changes throughout the book, including the addition of new topics and updated information on past topics.

Major new topics include coverage of:

- Chapter 2: CRISPR genetic technology
- Chapter 3: Effects of microbiome on the nervous system
- Chapter 4: Modified release formulations for drugs and dose dumping
- Chapter 5: Behavioral mechanisms of drug action; expanded coverage of brain reward circuitry
- Chapter 6: Cognitive enhancers
- Chapter 7: Risks of vaping
- Chapter 8: New chapter on depressants
- Chapter 9: Alcohol and drug interactions; alcohol myopia
- Chapter 10: Opioid epidemic; opioid prescribing
- Chapter 11: Cannabidiol; high-potency marijuana
- Chapter 12: Default-mode network and ego concepts
- Chapter 13: Psychedelic antidepressant drugs
- Chapter 14: MDMA-assisted psychotherapy for PTSD
- Chapter 15: Pharmacogenetics and antipsychotic drug effects

Here is a more detailed overview of what was added for the third edition.

- Chapter 1: Self-report questionnaires, additive and synergistic drug effects
- Chapter 2: Additional information about the enteric nervous system, gut microbiome, vagus nerve (including vagal nerve stimulation), and CRISPR genetic approaches
- Chapter 3: Source of serotonin outside the central nervous system, control of enterochromaffin cells by gut bacteria, role of microbiota in mental health, and probiotics for mental health
- Chapter 4: Expanded explanation of partial agonists, and tolerance and sensitization illustrated with dose-effect curves; modified release formulations for drugs and dose dumping
- Chapter 5: Concept of behavioral mechanisms of drug action, allostatic concept for opponent-process effects, and expanded coverage of brain reward circuitry, including mediation by D_1 versus D_2 receptors, triggers for relapse
- Chapter 6: Additional information on ephedra, introduced term *alkaloid*, note lisdexamfetamine (Vivance) as a compound similar to amphetamine, added figure for chemical structures of amphetamines, expanded coverage of synthetic cathinones, added figure for chemical structures of cathinones, content on D_1 and D_2 receptors in the rewarding effects of cocaine, added table for psychotropics used for psychostimulant addiction, and new section of the use of psychostimulants as cognitive enhancers and for treating ADHD
- Chapter 7: Content about snus, flavorings used in e-cigarettes, prevalence of vaping, risks of lung damage from vaping, absorption of nicotine from third-hand smoke, first report of cancer from tobacco use, anti-tobacco societies, material found in e-liquids for vaping, and addiction risks from e-cigarettes
- Chapter 8: Organized a new chapter dedicated to introducing depressant substances, which includes coverage of barbiturates, benzodiazepines, Z-drugs, GHB, and inhalants. Content includes characteristics of depressant drugs, role of GABA for effects of many depressants, and GABA_A receptor subtypes that GHB binds to
- Chapter 9: The chapter on alcohol was moved to Chapter 9. New content includes additional forms of alcohol administration, other enzymes involved in alcohol catabolism, low efficacy for first-pass metabolism, different types of aldehyde dehydrogenase, alcohol metabolism and sex differences, new section on alcohol-drug interactions, a table showing alcohol's pharmacological actions, alcohol's effect on tryptophan levels, alcohol myopia, role of NMDA receptors in alcohol blackout, alcoholic fatty liver disease, and chemical aversion therapy for alcohol addiction

- Chapter 10: Update on opioid abuse rates and overdose, discussion on prescribing rates for prescription opioids, changing recommendations on risks of opioid prescription drugs, plants that produce opioids (e.g., Kratom), prevalence of abuse of synthetic opioids, overview of tramadol, non-fentanyl-derived synthetic opioid drugs, itch from opioids, emergency use of naloxone (including Narcan spray) for opioid overdose, and concept of tolerance failure
- Chapter 11: Note the term *hemp*, ratios of THC to cannabidiol, discussion of state versus federal regulation of cannabinoids, note that anandamide means “internal bliss,” retrograde neurotransmission for 2-AG and anandamide with figure, information on cannabidiol pharmacology and effects, actions of cannabidiol on non-cannabinoid sites, effects of high-potency marijuana, discussion of marijuana use on adolescent development (e.g., cognition, IQ), amotivation and high-potency cannabis, and cannabidiol for treating epilepsy
- Chapter 12: New material includes a note about DMT and the pineal gland, updated prevalence data, coverage of the default mode network and how this system relates to Freud’s “ego” concepts (e.g., ego-dissolution), concept of set and setting for hallucinogenic effects, note about MDA in the MDMA section, coverage of muscimol, a note about *Alice in Wonderland*, and visual-evoked auditory response (for noisy gifs)
- Chapter 13: New material includes a note about severity of a disorder in the DSM, content about postpartum depression, actions of active metabolite of progesterone on GABA_A receptors, emotional blunting, content on trazodone, serotonin antagonist and reuptake inhibitors (SARI), psychedelic antidepressant drugs (e.g., Spravato), active placebos, depression severity and effectiveness of antidepressant drugs, Hamilton Depression Rating Scale, antidepressant-induced neurogenesis and the HPA axis, and mechanisms related to the ability for psychedelic drugs to reduce depression
- Chapter 14: Information added about general sedatives for anxiety, limitations for buspirone, beta blockers for anxiety, and MDMA-assisted psychotherapy for PTSD
- Chapter 15: Added content regarding prophylactic treatment (in the context of prodromal features of schizophrenia) and a section on pharmacogenetics and antipsychotic effects

Ancillaries

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Student Resources

SAGE Edge for Students provides a personalized approach to help students reach their coursework goals. The following resources are available on the open access version of the support site:

- Mobile friendly **Flashcards** to strengthen understanding of key terms and concepts.
- **Learning Objectives** to reinforce the most important materials.

Instructor Resources

SAGE Edge for instructors supports teaching by making it easy to integrate quality content and creates a rich learning environment for students. This password-protected site gives instructors access to resources that support and enhance their course. The following chapter-specific assets are available on the teaching site:

- A **Test Bank** provides a diverse range of questions as well as the opportunity to edit any question or insert personalized questions to effectively assess student progress and understanding.
- Editable, chapter specific **PowerPoint slides** offer complete flexibility for creating a multimedia presentation for the course.

Acknowledgments

I am thrilled to have my third edition developed by SAGE Publishing, which has a strong reputation for high-quality and trusted science textbooks. Writing a college textbook is a team effort. I appreciate all of the guidance, support, and advice from the acquisitions editor Abbie Rickard and for the editorial assistant for this book, Elizabeth Cruz. Emma Newsom, the book's content development editor, was instrumental in coordinating the design of figures and selection of photos for the book—a more organized person you will not meet. Laurie Pitman, the book's copy editor, spared readers from my numerous typos and grammatical errors found in my initial draft. Andrew Olson helped keep together all of the many moving parts of the production process. I certainly appreciate Scott Van Atta's impressive book cover and the efforts of Katherine Hepburn, the marketing manager of the book, to reach out to instructors who might have an interest in a psychopharmacology text.

I am especially grateful to the many expert reviewers who reviewed this book for accuracy and suggested many innovative directions for its content. Any errors or omissions in the text are entirely my own.

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To all: thank you!

About the Author



Dr. Adam Prus is a distinguished professor and head of the Department of Psychological Science at Northern Michigan University in Marquette, Michigan. He earned his PhD in psychology from Virginia Commonwealth University and a master's degree in psychology from Western Michigan University. While in graduate school, Dr. Prus also worked as a research technician in CNS diseases at a large pharmaceutical company. After earning his PhD, Dr. Prus investigated experimental antipsychotic drugs as a postdoctoral fellow at Vanderbilt University. Dr. Prus has published numerous original studies on psychoactive drugs, including studies funded by the National Institute on Mental Illness and private foundations. He is the recipient of several awards, including the Distinguished Faculty Award from Northern Michigan University and an Alumni Achievement Award from the Department of Psychology at Western Michigan University, and he was a Nominee for a Distinguished Professor of the Year Award from the Michigan Association of State Universities. At NMU, he directs the Neuropsychopharmacology Laboratory, where he enjoys mentoring undergraduate and graduate students who make him feel old when they later contact him for recommendation letters to faculty positions. When he is not teaching, training students, writing books, or conducting research, Dr. Prus spends time with his wife and two children, and together they enjoy outdoor activities in Michigan's Upper Peninsula, where NMU is located.

Introduction to Psychopharmacology

Chapter Outline

- Psychopharmacology
- Why Read a Book on Psychopharmacology?
- What Is a Drug?
- Psychoactive Drugs Are Described by Manner of Use
- Generic, Brand, Chemical, and Street Names for Drugs
- Drug Effects Correspond With Doses
- Pharmacodynamics, Pharmacokinetics, and Pharmacogenetics
- Objective and Subjective Effects of Psychoactive Drugs
- Study Designs and the Assessment of Psychoactive Drugs
- Validity and the Interpretation of Study Findings
- Ethical Considerations in Research
- From Actions to Effects: Therapeutic Drug Development

Learning Objectives

- Identify drugs in terms of their use and intended purpose
- Interpret drug effects based on dose
- Characterize the different pharmacological effects of drugs
- Appraise the quality of outcomes from scientific studies
- Assess the ethical conduct of drug studies using animal or human subjects
- Describe the process of therapeutic drug development

Psychoactive substances have made an enormous impact on society. Many people regularly drink alcohol or smoke tobacco. Millions of Americans take prescribed drugs for depression or anxiety. This book provides a thorough overview of the major classes of psychoactive drugs, including their actions in the body and their effects on behavior. In this first chapter, we learn some basic concepts about drugs and the ethical considerations involved in drug research.

Psychopharmacology

Psychopharmacology

Study of how drugs affect mood, perception, thinking, or behavior

Psychoactive drugs

Drugs that affect mood, perception, thinking, or behavior by acting in the nervous system

Psychopharmacology is the study of how drugs affect mood, perception, thinking, or behavior. Drugs that achieve these effects by acting in the nervous system are called **psychoactive drugs**. The term *psychopharmacology* encompasses two large fields: psychology and pharmacology. Thus, psychopharmacology attempts to relate the actions and effects of drugs to psychological processes.

A psychopharmacologist must have knowledge of the nervous system and how psychoactive drugs alter nervous system functioning. A psychopharmacologist can be a medical practitioner, like a psychiatrist, who specializes in prescribing psychoactive medication, or a scientist who studies psychoactive drugs. This approach defines the structure of this textbook. First, this book provides an overview of cells and structures of the nervous system. Second, it covers the basic principles of pharmacology. After this, we apply our knowledge of the nervous system and pharmacology to understand the actions and effects of psychoactive drugs, beginning with recreational and abused drugs and ending with therapeutic drugs for treating mental disorders.

Psychopharmacology is not the only term used to describe this field (**Table 1.1**). Another term is *behavioral pharmacology*. Many consider behavioral pharmacology as synonymous with psychopharmacology, but others classify *behavioral pharmacology* as part of the subfield of psychology called *behavior analysis*. In this respect, drugs serve as behaviorally relevant stimuli just like other stimuli in behavior analytic models. *Neuropsychopharmacology* is another term for psychopharmacology. The *neuro* prefix represents the nervous system. Although the terms are similar, the neuropsychopharmacology field has a particular emphasis on the nervous system actions of drugs.

TABLE 1.1 Names Used to Describe Psychopharmacology

Field	Description
Psychopharmacology	The study of how drugs affect mood, perception, thinking, or behavior.
Behavioral pharmacology	The study of how drugs affect behavior. Sometimes, behavioral pharmacologists emphasize principles used in the field of behavior analysis.
Neuropsychopharmacology	The study of how drugs affect the nervous system and how these nervous system changes alter behavior.

Why Read a Book on Psychopharmacology?

Psychopharmacology is an important part of modern psychology. First, psychoactive drug use is highly prevalent. In the United States, for example, consider the following:

- 12.7 percent of those 12 and older currently use an antidepressant drug (Pratt, Brody, & Gu, 2017).
- More than 17 million use an anti-anxiety (i.e., anxiolytic), sedative, or hypnotic drug.
- More than 29 million use a prescribed pain-relieving drug (National Center for Health Statistics, 2018).

When we add recreational drugs to the list, psychoactive drug prevalence in the United States increases further:

- More than half of those 18 and older consume alcohol (National Institute on Alcohol Abuse and Alcoholism, 2018).
- 47.5 percent of those 12 and older have used cannabis at some point in their lives (National Institute on Drug Abuse, 2018).
- More than 72 million individuals use tobacco products (Substance Abuse and Mental Health Services Administration [SAMHSA] and Center for Behavioral Health Statistics and Quality, 2017).

The World Health Organization (WHO) also reports high rates of psychoactive drug use internationally (WHO, 2012). To understand typical human behavior in the modern world, the sheer prevalence of drug use requires that we understand how drugs affect the way we think and function.

The second reason for reading this text is that the statistics just presented show how many of us are consumers of psychoactive substances; as consumers, we should know about the substances we ingest. Greater knowledge of psychoactive substances improves patient understanding of prescribed medical treatments and health implications of taking recreational and abused substances.

Third, you will come to understand how psychoactive substances provide important tools for understanding human behavior. For example, the actions of antidepressant drugs led to understanding the roles that certain neurotransmitters and brain structures play in depression. Researchers use many experimental psychoactive drugs entirely as pharmacological tools for understanding brain function and behavior. Fourth, you will see how psychopharmacologists help to develop psychoactive treatments for psychological disorders.

What Is a Drug?

In a way, you know a drug when you see one. After all, the term *drug* is part of our everyday language. We take drugs for headaches, drugs for infections, drugs for mood, and drugs for virtually any other ailment or disorder. We even take drugs to prevent disorders. But, what exactly is a drug?

Drug

An administered substance that alters physiological functioning

To provide a simple definition, a **drug** is an administered substance that alters physiological functioning. The term *administered* indicates that a person takes or is given the substance. The phrase “alters physiological functioning” implies that the substance must produce some change in physiological processes.

This definition has challenges. The term *administered*, for example, excludes substances made naturally in the body. The neurotransmitter dopamine is made in the nervous system and elicits important changes in nervous system functioning. However, hospital physicians may administer dopamine to a patient in order to elevate heart rate. In this context, dopamine is an administered substance that alters physiological functioning. Yet, the same dopamine is made in the body—distinguishing the two leads us to call dopamine a drug when a practitioner administers it and call dopamine a neurotransmitter when the brain produces it.

Along the same lines, many of us take vitamins to ward off disease and improve health. We administer vitamins to ourselves. Why not call *vitamins* drugs? We simply describe them as vitamins (**Figure 1.1**). Nor do we describe herbal remedies as drugs despite their physiological effects.

FIGURE 1.1 **Examples of Substances Used**

(a) Antidepressants (b) Vitamins (c) Vaping (d) Sniffing glue

(a)



Copyright iStock Photo/svetikd

(b)



gospinodesign/
Shutterstock.com

(c)



Copyright iStock Photo/
diego_cervo

(d)



Jan H Andersen/Shutterstock.com

The term *substance* in the definition of drug also lacks a precise description. The antidepressant in Panel A for Figure 1.1 has the appearance of a drug, but the substances in the other three panels seem less like drugs. Each substance, however, exhibits physiological changes in the body.

The emphasis on physiological functions also has limitations. Certainly, drugs produce changes in the body—but is food a drug? After all, food also produces physiological changes in the body.

Do drugs have a certain appearance? Drugs come in a variety of different forms, including pills, liquids, and powders. Most people consider nicotine a drug, although nicotine molecules reside within tar particles inhaled when smoking tobacco or in an e-liquid when vaped. Some may sniff certain types of glue, the vapors of which contain chemicals such as toluene. In this case, drugs also come in vapor form.

Thus, although *drug* is a common term, we must not restrict our perception of a drug to a specific form or usage in psychopharmacology. Doing so risks excluding nonconforming substances that may have powerful effects for altering behavior. As presented in Chapter 5, for example, thinking of food as a drug provides a useful means of understanding food addiction.

STOP & CHECK

Stop & Check questions provide a quick way to self-assess your comprehension of the material. These questions pertain to main points and are provided throughout the chapters of this book.

1. In general, how prevalent is psychoactive drug use?
2. What is the definition of a drug?

1. Both therapeutic and recreational drugs are highly prevalent in society. Alcohol, caffeine, and nicotine are highly prevalent, as are medications for anxiety, depression, and pain. 2. A drug is an administered substance that alters physiological functioning. A more precise term is lacking, but it's helpful to think critically about the limitations of what we consider a drug to be in order to appreciate the forms a psychoactive substance may take and ways a substance might affect us.

Psychoactive Drugs Are Described by Manner of Use

Psychoactive drugs broadly fall into two categories: those intended for instrumental use and those intended for recreational use. The major distinction between these categories is a person's intent or motivation for using the substance. **Instrumental drug use** consists of using a drug to address a specific purpose. For example, someone may take an antidepressant drug such as Prozac for the purpose of reducing depression. Further, most adults consume caffeinated beverages like coffee to help them wake up in the morning, another socially acceptable purpose. In psychopharmacology, instrumental use often occurs with **psychotropic drugs**—drugs used for treating disorders—for treating mental disorders such as depression and schizophrenia.

Instrumental drug use

Using a drug to address a specific purpose

Psychotropic drug

Drug used to treat a psychological disorder

Recreational drug use

Using a drug entirely to experience the drug's effects

Drug misuse

Recreationally using a drug that has accepted instrumental uses

Brand name (or trade name)

A trademarked name a company provides for a drug

Generic name

A nonproprietary name that indicates the classification for a drug and distinguishes it from others in the same class

Chemical name

A name that details a drug's chemical structure

Recreational drug use refers to using a drug entirely to experience its effects. For example, recreational use of alcohol may consist of drinking alcohol purely to experience its intoxicating effects. Many drugs can be misused for recreational purposes. The term **drug misuse** applies to drugs that are intended for instrumental purposes but are instead used recreationally. For example, cough syrups that contain codeine or dextromethorphan are misused recreationally to achieve mind-altering effects such as euphoria or hallucinations.

Recreational use may lead to dependence. During *drug dependence*, a user also experiences a need or urge to continue using a substance and has difficulty reducing use of the substance. Chapter 5 expands upon the clinical characteristics of drug dependence.

Generic, Brand, Chemical, and Street Names for Drugs

Individual drugs have different names. For example, people commonly take Tylenol to treat headaches. Although the name *Tylenol* is the most widely known name, the drug is also known by a different name: acetaminophen. We refer to Tylenol as its *brand name* and acetaminophen as its *generic name*.

Nearly all therapeutic drugs have a generic name and at least one brand name. A pharmaceutical company that develops and markets a drug provides both trade and generic names, each for different purposes. A drug's **brand name** (or **trade name**) is a trademarked name a company provides for a drug. Sometimes, a trade name is designed to be memorable or emotion provoking. For example, common sleep aids include *Ambien* and *Lunesta*. The name *Lunesta* resembles the word *luna*, meaning “moon,” a symbol for night. Plus, the word *Lunesta* is a soft sounding name, giving a relaxing connotation to the drug.

A drug's **generic name** is a nonproprietary name that indicates the classification for a drug and distinguishes a drug from others in the same class. For example, note the generic names of the following antipsychotic drugs: chlorpromazine, clozapine, and olanzapine. All three of these drugs end in *a* followed by a consonant and then the suffix *-ine*. We can guess that drugs with *-apine* or *-azine* in their names act as antipsychotic drugs. The names also reflect something about these drugs' chemical structures. The *-ine* suffix corresponds to an amine chemical group in their structures. Moreover, the first two drugs, chlorpromazine and clozapine, have chloride molecules in their structures. Generic names do not follow hard rules and cannot be relied upon entirely to inform us about a drug's classification or important features of its chemical structure. But as shown in this example, they can provide ways to show how drugs organizationally compare to others.

Scientific reports normally refer to a drug's generic name. In these cases, the generic name is sometimes followed by the drug's brand name in parentheses. Moreover, brand names are capitalized. For example, a report might read “Physicians prescribe zolpidem (*Ambien*) for insomnia.” The generic name is zolpidem, and its brand name is *Ambien*.

Drugs also have chemical names. A drug's **chemical name** details a drug's chemical structure. For example, the chemical name for zolpidem is “N,N-dimethyl-2-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]acetamide.” It's beyond the

TABLE 1.2 Examples of Street Names for Selected Drugs

Drug	Street Name
Amphetamines	Bennies, black beauties
Benzodiazepines	Downers
Cocaine	Coke, crack
Dextromethorphan (used in cough syrup)	Robo, triple C
Methamphetamine	Meth, crystal
MDMA	Ecstasy
LSD	Acid
Phencyclidine	PCP, angel dust

scope of this textbook to cover what the many components of this name mean—general chemistry and organic chemistry textbooks can tell you that. For our purposes, we can appreciate that the chemical name tells anyone with sufficient chemistry education what zolpidem’s chemical structure looks like. The rules used for writing a drug’s chemical name come from the *International Union of Pure and Applied Chemistry* (or IUPAC for short), an international, independent organization of chemists focused on advancing the chemical sciences.

Recreational drugs are often referred to by **street names**. Street names are given by those who use, sell, or illegally make recreational drugs. Street names can serve as benign-sounding aliases. For example, *ADAM* is a reference to the drug MDMA (an abbreviation of 3,4-methylenedioxymethamphetamine). Street names may also reflect the drug’s effects. For example, the drug MDMA is also known as *ecstasy*, which connotates pleasurable effects. **Table 1.2** lists common recreational substances and some known street names.

Street name

An alternative name applied to a recreational or abused substance

Drug Effects Correspond With Doses

The strength of a drug’s effects depend on a drug’s dose. **Dose** is a ratio of the amount of drug per an organism’s body weight. For example, the dose of a drug given to a laboratory rat might be 1.0 gram of drug per kilogram body weight. This is written as 1.0 g/kg. To put this into context, if a rat weighed 1 kg—an incredibly large rat—then it would receive 1 gram of drug. If, instead, a rat weighed 0.3 kg (a more reasonably sized rat), then it would receive 0.3 grams of drug.

For over-the-counter medications like Tylenol, the dosing instructions assume an average adult’s body weight. If the instructions describe something like “Take one to two 325 mg tablets,” then the “one to two” range refers to differences in body weight between adults. A larger individual might require two tablets, whereas a smaller individual might only require one tablet. A doctor’s office records your weight, in

Dose

Ratio of the amount of drug per an organism’s body weight

Dose-effect curve

Depicts the magnitude of a drug effect by dose

ED₅₀

Value that represents the dose at which 50 percent of an effect was observed

part, to calculate drug dosing. If the doctor prescribes a medication, she needs to know the dose of a drug to prescribe based on your body weight.

Generally, the higher a drug's dose, the greater its effects. Researchers determine the effects of drugs by evaluating a range of different doses. This information is plotted on dose-effect curves. A **dose-effect curve** (or **dose-response curve**) depicts the magnitude of a drug effect by dose. **Figure 1.2** presents two drugs plotted on dose-effect curves.

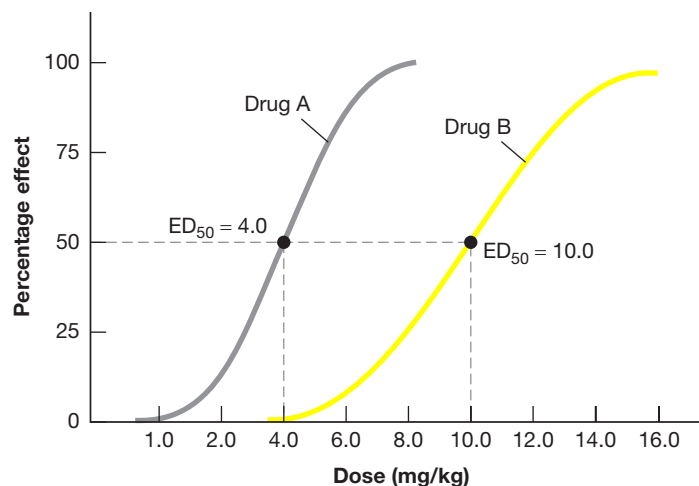
For each drug in Figure 1.2, lower doses produce weaker effects and higher doses produce stronger effects. Both drugs produce a full, 100 percent effect at a high enough dose. Yet, notice that both drugs achieve full effectiveness at different doses. For drug A, 100 percent effectiveness occurs at an 8.0 mg/kg dose, whereas 100 percent effectiveness for drug B occurs at a 16.0 mg/kg dose. In fact, the entire dose-effect curve for drug A is located to the left of drug B (i.e., the curves do not overlap).

To describe the position of a dose-effect curve, researchers calculate an ED₅₀. An **ED₅₀** is a value that represents the dose at which 50 percent of an effect was observed.¹ The “ED” stands for “effective dose.”

As shown in Figure 1.2, drug A's ED₅₀ is 4.0 mg/kg. This corresponds to a dose that matches with the 50 percent effect point on the dose-effect curve. Nothing prevents a researcher from determining other ED values if she chooses. Perhaps in her particular study, knowing, say, an ED₇₅ (i.e., dose at which 75 percent of the effect

FIGURE 1.2 **Dose-Effect Curves**

Both drugs shown here achieve 100 percent effectiveness, but at different doses. Drug A is the most potent because it achieves these effects at lower doses than drug B. For drug A, the dose at which 50 percent of the effect occurs (ED₅₀) is 4.0 mg/kg. The ED₅₀ for drug B is 10.0 mg/kg.



¹Alternatively, an ED₅₀ value can reflect a dose at which 50 percent of the subjects exhibited a full effect.

was observed) or ED_{15} (i.e., dose at which 15 percent of the effect was observed), would be important. We tend to calculate ED_{50} values because they represent a middle point on the curve and thus are generally more useful for conveying a drug's effective-dose range than other ED values.

ED_{50} s provide a means for comparing the potency of drugs. **Potency** refers to the amount of drug used to produce a certain magnitude of effect. Describing a drug as “highly potent” means that drug effects occur at low doses. The hallucinogen lysergic acid diethylamide, better known as LSD, is considered highly potent, because very small amounts of LSD—as little as 0.02 mg, so small that users may need to lick LSD powder from the glue side of a postage stamp—produce hallucinations (Greiner, Burch, & Edelberg, 1958). Researchers also use potency to compare different drugs that produce similar effects.

Potency

Amount of drug used to produce a certain level of effect

Consider again the drugs in Figure 1.2. Drug A reaches the same magnitude of effects as drug B, but drug A does so at lower doses. Thus, drug A has a higher potency than drug B. By representing a dose-effect curve, an ED_{50} allows a way to calculate the relative level of potency between different drugs. Drug A has an ED_{50} of 4.0 mg/kg, and drug B has an ED_{50} of 10.0 mg/kg. The potency difference is calculated from dividing drug B, the compound with the highest ED_{50} , by drug A, the compound with the lowest ED_{50} . In this example, we find drug A to be 2.5 times more potent than drug B.

When developing a new therapeutic drug, researchers must determine a drug's dose that causes unacceptable adverse effects. We refer to this dose as a *toxic dose* and can produce toxic dose-effect curves using laboratory animals as subjects, just as we can produce therapeutic dose-effect curves. Researchers and regulators understand that no drug is free from a host of potential adverse effects, but certain doses of any drug will produce adverse effects too severe to justify giving to a patient even if the same dose produced therapeutic effects.

As noted previously, toxicity studies also produce dose-effect curves. The ED_{50} for toxic dose-effect curves is referred to as a TD_{50} (TD stands for *toxic dose*). In this case, we interpret a TD_{50} as the dose at which 50 percent of the subjects had the particular toxic effect in question (the one too severe to risk producing in humans). TD_{50} values allow for the determination of a therapeutic index.

A **therapeutic index** conveys the distance between toxic and therapeutic doses as a ratio of a drug's toxic dose-effect curve value relative to a therapeutic dose-effect curve value. One way to calculate a therapeutic index is to divide a TD_{50} by an ED_{50} . A therapeutic index answers this question: How different is a dose that causes toxic effects in half of the subjects from a dose of the same drug that produces therapeutic effects in half of the subjects?

Therapeutic index

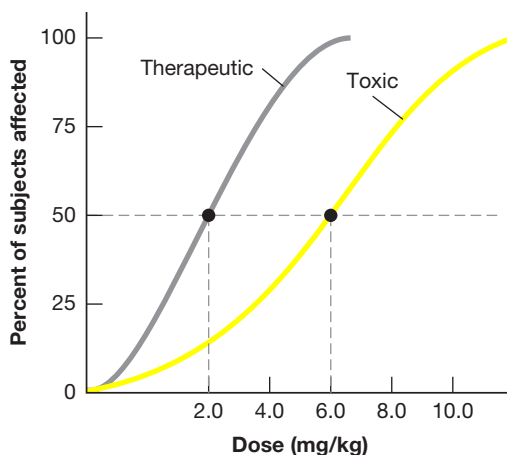
Ratio of a drug's toxic dose-effect curve value relative to therapeutic dose-effect curve value

Although ED_{50} and TD_{50} values provide a means to calculate therapeutic indexes, these values are not ideal for identifying safe drugs. **Figure 1.3** shows a drug's therapeutic dose-effect curve and toxic dose-effect curve. The TD_{50} dose (6.0 mg/kg) is three times greater than the ED_{50} dose (2.0 mg/kg). Is that good? Notice that approximately 15 percent of all subjects experience toxic drug effects at the ED_{50} dose. If you look further, a fully effective therapeutic dose caused toxic effects in half of the subjects. This is clearly not a safe drug!

To avoid any overlapping therapeutic and toxic dose-effect curves, drug developers adopt a far more conservative calculation for a therapeutic index, referred to

FIGURE 1.3 Therapeutic and Toxic Dose-Effect Curves

Is this drug safe to use? This drug does produce therapeutic effects at doses lower than those that produce lethal effects. In fact, the TD_{50} ($TD_{50} = 6.0$ mg/kg) is three times greater than the ED_{50} ($ED_{50} = 2.0$ mg/kg). Yet, notice that at the ED_{50} (2.0 mg/kg), approximately 15 percent of the subjects experienced toxic drug effects. At a dose at which full therapeutic effects were shown (6.0 mg/kg), approximately 50 percent of the subjects experienced toxic drug effects. Thus, although the therapeutically effective doses are lower than the toxic doses, many subjects will experience severe adverse effects—clearly this is not a safe drug to use.



Certain Safety Index

A therapeutic index calculated by dividing a TD_1 by an ED_{99} .

as a Certain Safety Index. We calculate a **Certain Safety Index** by dividing a toxic dose that caused toxicity in only 1 percent of the subjects—referred to as a TD_1 —by a dose that achieved a 99 percent therapeutic effect—an ED_{99} . Large therapeutic indexes derived from this safer calculation describe very separate therapeutic and toxic dose-effect curves.

The U.S. Food and Drug Administration (FDA) and similar regulatory bodies in other countries require safe therapeutic indexes for drugs they approve. However, this is not to say that every drug on the market has a large therapeutic index. For example, the mood stabilizer lithium has a lethal dose near the therapeutic dose, and for some individuals, taking only twice the recommended dosage might lead to severe adverse effects.

Drugs taken together may have additive or interaction effects. If two drugs produce the same effect, the two given together might produce a greater effect. One type of drug interaction effect is an *additive effect*. For **additive drug effects**, the magnitude of the combined drug effect is the sum of each drug's effect alone. For example, if drug A alone produced an increase in systolic blood pressure of 5 mmHg and drug B produced an increase in systolic blood pressure of 10 mmHg, then combined, an additive effect would be a 15 mmHg increase. Another type of drug interaction is *synergism*. **Synergistic drug effects** consist of a magnitude of effect beyond the sum of each drug's effect. From the previous example, drug synergism

Additive drug effects

The magnitude of the combined drug effect is the sum of each drug's effect alone

Synergistic drug effects

The magnitude of the combined drug effect is beyond the sum of each drug's effect alone

might be demonstrated if combining both drugs led to a 20 mmHg increase—well beyond the sum of each drug’s effects.

STOP & CHECK

1. What determines whether a drug is a therapeutic drug or a recreational drug?
2. What are the two different names provided for therapeutic drugs?
3. What is a dose?
4. What is the safest approach for calculating a therapeutic index?

1. The manner of usage. Individuals use therapeutic drugs instrumentally toward treating a disorder or ailment, whereas individuals take recreational drugs entirely to experience the drug’s effects. 2. Therapeutic drugs are provided a generic name, which refers to the organizational fit of a drug with similar acting drugs, and a trade name, which is the company’s brand name for the drug. 3. A dose is a ratio of the amount of drug per amount of body weight. Most of the instructions provided with over-the-counter drug packages advise taking pills based on an average adult weight. 4. A Certain Safety Index provides the safest approach for calculating a therapeutic index by dividing a toxic dose for 1 percent of subjects, referred to as a TD_{01} , by a 99 percent effective dose, referred to as an ED_{99} . When this calculation produces large therapeutic indexes, the toxic doses are much higher than therapeutically effective doses.

Pharmacodynamics, Pharmacokinetics, and Pharmacogenetics

Pharmacodynamics and pharmacokinetics represent two major areas in pharmacology. Pharmacodynamics refer to the physiological biochemical actions of drugs. For psychoactive drugs, this includes the drug’s actions on the nervous system. Most addictive recreational drugs, for example, act on the brain’s reward pathways to produce pleasurable effects. Chapter 4 provides an overview of many pharmacodynamic processes.

Pharmacokinetics refers to how drugs pass through the body. This field considers different ways to administer a drug, how long a drug stays in the body, how well the drug enters the brain, and how it leaves the body. For example, pharmacokinetic properties explain why nicotine reaches the brain more rapidly by smoking tobacco than by chewing tobacco.

Although pharmacodynamics and pharmacokinetics define the classical broad categories in pharmacology, a subfield of pharmacology—pharmacogenetics— affects both categories. **Pharmacogenetics** is the study of how genetic differences influence a drug’s pharmacokinetic and pharmacodynamic effects. This field provides the basis for differences in drug response between individuals. As we well know, a single therapeutic drug does not work for everyone. In fact, for psychoactive therapeutic drugs such as antidepressants, a physician may need to switch through several different medications for a patient until finding an effective one.

Pharmacokinetics

The physiological and biochemical actions of drugs

Pharmacogenetics

The study of how genetic differences influence a drug’s pharmacokinetic and pharmacodynamic effects

Genetically related differences in drug responsiveness may affect a drug's actions in the nervous system or passage through the body. In particular, some individuals are “fast metabolizers” for many drugs, meaning that certain drugs are quickly broken down in their livers. When this occurs, less of a drug stays intact in the body, resulting in weaker drug effects. Knowing that a patient is a fast metabolizer for certain drugs enables a physician to alter one's treatment plan. For example, a physician may prescribe a separate treatment that reduces metabolism of the drug or may prescribe an alternative drug that the person will metabolize more slowly.

Objective and Subjective Effects of Psychoactive Drugs

Objective effects

Pharmacological effects that can be directly observed by others

Subjective effects

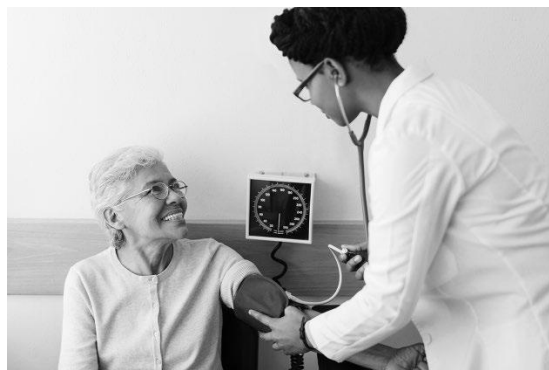
Pharmacological effects that cannot be directly observed by others

To characterize the spectrum of a drug's pharmacological effects, researchers must measure the drug's objective and subjective effects. **Objective effects** are pharmacological effects that can be directly observed by others. In other words, a researcher can independently measure the drug's effects. For example, psychostimulant drugs can affect blood pressure. A researcher can objectively measure this by using a blood pressure cuff (**Figure 1.4**).

Subjective effects are pharmacological effects that cannot be directly observed by others. In other words, we cannot observe or measure another's drug experience (see Box 1.1). The inability to independently observe subjective effects has certain scientific limitations. In particular, a drug's subjective effects may vary from person to person. To address this, researchers must develop a consensus about a drug's effects among many individuals and assume that this consensus accurately reflects the drug's effects for anyone else who may take the drug.

FIGURE 1.4 Objective and Subjective Drug Effects

Objective effects (left) are pharmacological effects that can be directly observed by others, whereas subjective effects (right) are pharmacological effects that cannot be directly observed by others; instead, a study participant may describe a drug's effects to a researcher or rate a drug's effects on a questionnaire.



BOX 1.1

INSTRUMENTS USED FOR STUDYING SUBJECTIVE EFFECTS IN HUMANS

A drug's subjective effects help researchers to understand a drug's therapeutic benefits or its potential for recreational use. The measure of subjective effects in humans relies almost entirely on *self-report questionnaires*. A self-report questionnaire for drug effects consists of a study participant noting the features and degrees of effects felt from taking a substance. When a questionnaire has a valid use in clinical characterizations or diagnoses, the questionnaire may also be referred to as an *instrument*. Commonly, self-report questionnaires use *Likert scales*. For a Likert scale, a participant rates the magnitude of attitudes or perceptions about a description of a feeling, viewpoint, or event. Often, Likert scales present an individual with a range of choices, from *strongly disagree* to *strongly agree* or similar terms.

In practice, we find Likert scales employed to assess the degree of feelings a person experiences or

specific effects from a psychoactive drug. A well-known instrument for gauging an individual's current mood state is the *Profile of Mood States Questionnaire*, often referred to by the acronym POMS. A clinician can use the POMS to rate a client's degree of agreement with a feeling or emotion, using terms such as "energetic" or "on edge" (**Box 1.1 Figure 1**). Rating options for these statements range from "not at all" to "extremely" on the POMS (McNair, Lorr, & Droppleman, 1971). As an example, a study conducted by Johanson and Uhlenhuth (1980) used the POMS for study participants they treated with the anti-anxiety medication diazepam (Valium; a type of benzodiazepine covered later in this book). After one to three hours following administration, respondents endorsed feelings related to fatigue and confusion and were less likely to endorse feelings related to vigor.

BOX 1.1 FIGURE 1

Researchers use questionnaires and psychological instruments to assess the subjective effects of psychoactive substances.

Below is a list of words that describe feelings people have.

	Not at All	A Little	Moderately	Quite a Lot	Extremely
Tense	0	1	2	3	4
Angry	0	1	2	3	4
Worn out	0	1	2	3	4
Unhappy	0	1	2	3	4
Proud	0	1	2	3	4
Lively	0	1	2	3	4
Confused	0	1	2	3	4

(Continued)

(Continued)

	Not at All	A Little	Moderately	Quite a Lot	Extremely
Sad	0	1	2	3	4
Active	0	1	2	3	4
On edge	0	1	2	3	4
Grouchy	0	1	2	3	4
Ashamed	0	1	2	3	4
Energetic	0	1	2	3	4
Hopeless	0	1	2	3	4
Uneasy	0	1	2	3	4
Restless	0	1	2	3	4
Unable to concentrate	0	1	2	3	4
Fatigued	0	1	2	3	4
Competent	0	1	2	3	4
Annoyed	0	1	2	3	4
Discouraged	0	1	2	3	4
Resentful	0	1	2	3	4
Nervous	0	1	2	3	4
Miserable	0	1	2	3	4

For studies involving recreational substances, researchers often assess how much participants enjoy the effects of a drug. To do this, many studies use a “liking” scale, asking participants to rate, from strongly disliking to strongly liking, the effects felt from a substance administered to them by the researchers (in a safe, controlled laboratory setting). These scales may have labels drawn on a horizontal line, allowing a study volunteer to mark the degree of liking for a drug’s effects on the line. For this approach, we refer to these instruments as having *visual analog scales*. For example, Soria and colleagues (1996) used visual analogy scales to assess the subjective effects of nicotine in smokers and nonsmokers. Smokers, on average, placed marks around 50mm for lines that ran from 0mm to 100mm to rate nicotine’s

“good effects.” Nonsmokers, on the other hand, placed marks around 15mm.

Researchers also can ask how a drug’s effects compare to those produced by other substances. One of these instruments is the *Addiction Research Center Inventory* (commonly referred to by the acronym ARCI), which consists of questions that coincide with effects produced by classic recreational or abused substances. For example, Soria and colleagues (1996) used the ARCI in their assessments of nicotine in smokers and nonsmokers. Smokers reported that nicotine produced positive effects, somewhat like morphine and benzedrine, and nonsmokers reported disorienting effects and “weird feelings,” somewhat like the drug lysergic acid diethylamide (better known as LSD).

Despite some scientific limitations, a psychoactive drug's subjective effects are often more important for understanding why a drug is used than its objective effects. Subjective effects explain the purpose of recreational and addictive drug use. Subjective effects also explain the therapeutic value of antidepressant, anti-anxiety, and antipsychotic drugs. Only the patient can say whether medications truly help to reduce depressed feelings, anxiety, and paranoid thoughts.

STOP & CHECK

1. How do pharmacodynamic effects differ from pharmacokinetic effects?
2. How might pharmacogenetic factors alter a person's response to a psychoactive drug?
3. What is the challenge in studying subjective drug effects?

1. Pharmacodynamic effects refer to the biological effects of a drug, whereas pharmacokinetic effects refer to the movement of a drug through the body, including a drug's entry into the nervous system. 2. One's genetic makeup may alter a drug's passage through the body or alter a drug's actions in the nervous system. 3. Subjective effects represent an individual's personal and non-publicly observable effects from a drug, including how a person feels after taking the drug. We must rely entirely on self-reported drug effects. Yet for recreational drugs, subjective effects are the most important to characterize and understand.

Study Designs and the Assessment of Psychoactive Drugs

The logic behind study designs provides the means to assess a drug's behavioral effects. Studies attempt to answer scientific questions about drug effects and the nervous system by using dependent and independent variables. A **dependent variable** is a study variable measured by a researcher. In psychology, dependent variables usually consist of behavioral measures, such as how many words an individual recalls from a list or an evaluation of one's level of depression.

Independent variables are study conditions or treatments that may affect a dependent variable. Independent variables for the previous examples might include teaching individuals a memorization technique or providing depressed individuals an antidepressant drug. In each case, study researchers sought to determine whether an independent variable produced changes to a dependent variable.

Dependent variable

A study variable measured by a researcher

Independent variable

Study conditions or treatments that may affect a dependent variable

Experimental study

Study in which investigators alter an independent variable to determine whether changes occur to a dependent variable

Experiments

Research studies fall into two categories: experimental studies and correlational studies (see **Table 1.3**). In an **experimental study**, investigators alter an independent variable to determine whether changes occur to the dependent variable. For example, many clinical studies use experiments to evaluate drug effects. In a standard

TABLE 1.3 Correlational and Experimental Studies

Study Type	Description
Correlational study	No alteration of study conditions. Changes in study variables are observed, and relationships are inferred.
Experimental study	Researchers alter a study's independent variable and observe changes in a dependent variable. Experiments can identify causal relationships between an independent variable and a dependent variable.

Placebo

Substance identical in appearance to a drug but physiologically inert

Single-blind procedure

When researchers do not inform study participants which treatment or placebo they received

Double-blind procedure

When neither participants nor investigators know the treatment assignments during a study

Open-label studies

Assignment of study treatments without using blinded procedures

Correlational study

Study in which an investigator does not alter the independent variable but associates changes with the dependent variable

experimental study design, individuals sharing a type of disorder are separated into two groups: a control group and a treatment group. The treatment group receives the treatment, and the control group does not. Instead, the control group may be given a **placebo**, or a substance identical in appearance to a drug but physiologically inert. If individuals in the treatment group improve over the course of this study and those in the control group do not, then researchers attribute improvements to the treatment. Experiments such as these indicate that the independent variable *caused* changes to the dependent variable.

Experiments use random sampling to assign participants to study groups. Through random assignment, researchers seek to achieve groups that have similar characteristics. Many experiments also use blinding procedures to eliminate potential biases by study participants or investigators. In a **single-blind procedure**, researchers do not inform study participants which treatment or placebo they received. To provide informed consent, study investigators provide participants a description of treatments that might be administered, as well as the potential for placebo administration, but they do not identify the assigned treatment to participants during the study.

In a **double-blind procedure**, neither the participants nor the investigators know the treatment assignments during the study. These procedures not only prevent potential biased responses from participants, but also prevent potential biased judgments by study investigators. Although researchers consider blinded procedures important for quality experimental studies, not all experiments allow for blinded procedures.

In clinical research, **open-label studies** refer to the assignment of study treatments without using blinded procedures. Open-label studies apply to situations in which disguising study medications may have serious ethical consequences or be impractical. For example, many cancer clinical trials use open-label procedures because withholding a potential effective treatment from cancer patients by using a placebo might have serious health consequences.

Correlational Studies

In a **correlational study**, an investigator determines if the changes in one variable are associated with changes to another variable. Generally, a correlational study

identifies one of the variables as an independent variable², but the conditions of this variable are not altered like they are for an experiment. For example, to study the effects of long-term MDMA use on memory, a researcher might recruit participants who used MDMA and then measure each participant's ability to recall words from a list. We could use the duration of MDMA use as the *independent variable*, and each participant's level of memory serves as the *dependent variable*. The investigators did not alter the independent variable, but instead studied duration of MDMA use and memory ability as conditions that already existed. Researchers might infer a relationship between MDMA use and memory if long-term MDMA users exhibited poor word recall and if infrequent MDMA users exhibited good word recall. But, it is important that correlational studies do not indicate that a variable *causes* changes to another variable.

Validity and the Interpretation of Study Findings

Say you conducted an experiment and found that a newly developed drug reduced symptoms of depression. Great news, but what can you actually infer from these study results? This question addresses the quality of study procedures, the appropriate choice of species tested, the ability to extend these findings to other individuals with the disorder, and many other possible issues. Researchers must address such questions in order to draw *valid inferences* from a study's findings (Elmes, Kantowitz, & Roediger, 2006).

College courses on research methodology and design devote considerable time to discussing valid inferences, and they do so in much greater detail than is considered here. For our interests, let's consider some basic types of validity and think about how the issue of validity can affect studies in psychopharmacology. The types of validity we discuss are internal validity, external validity, face validity, construct validity, and predictive validity (**Table 1.4**).

TABLE 1.4 Types of Validity

Validity	Description
Internal validity	Adequacy of controlling variables that may influence a dependent variable
External validity	Ability to extend findings beyond study conditions
Face validity	Test appears to measure what a researcher considers it to measure
Construct validity	How well a study's findings relate to the underlying theory of a study's objectives
Predictive validity	Ability of model to predict treatment effects

²Alternatively, correlational studies can use the term *predictor* instead of *independent variable*.

Internal validity

Control of variables with potential to influence a dependent variable

Internal validity refers to the control of variables with potential to influence a dependent variable. Ideal experiments arrange conditions so that only changes to the independent variable will cause changes to the dependent variable. Without appropriately arranging conditions, other variables, referred to as *confound variables*, can cause changes to the dependent variable.

For example, a study designed to test new drugs for depression may involve patients checking in with a clinic physician every morning. After several weeks, the study results indicate a reduction in depression. Might this study have confound variables?

The daily clinic visits are a potential confound variable. The act of talking to a physician daily about depressive symptoms in a clinical setting may have been sufficient to reduce depressive symptoms in this study. Without considering potential confound variables such as these, study investigators risk wrongly concluding that an experimental drug produces therapeutic effects.

To avoid potential confound variables, researchers blind participants to the study medications, and they may also assign a placebo to a participant group. Placebo groups control for many confound variables. If placebo-treated patients also exhibited reduced depression, then we conclude that variables other than the study medication caused reductions in depression.

External validity

Refers to how well study findings generalize beyond the study conditions

External validity refers to how well study findings generalize beyond the study conditions. For example, many clinical antidepressant studies examine only adults. Such studies have poor external validity for antidepressant effects in children, because they provide no evidence of an antidepressant's effectiveness in children.

External validity also presents limitations for predicting treatment effects in humans from studies conducted in animals. One example of this occurred with the drug thalidomide in the 1950s. Thalidomide induced sleep and prevented nausea and vomiting. For these reasons, pregnant women received thalidomide to aid with severe morning sickness. However, thalidomide proved harmful for human fetal development. By 1962, nearly 10,000 babies had been born with missing fingers, toes, and limbs after exposure to thalidomide during pregnancy.

Why did pharmacologists consider this a safe drug for pregnant women? In humans, thalidomide was metabolically transformed into a **teratogen**, a substance harmful to a fetus.

Teratogen

Substance harmful to a fetus

This metabolic transformation did not occur in mice, the animals studied in thalidomide experiments. Had drug developers tested thalidomide in rabbits, which do convert thalidomide into this teratogen, doctors would not have prescribed thalidomide to pregnant women. Thus, in this case, rabbits, not mice, provide proper external validity for this property of thalidomide (Goldman, 2001). Proper drug screening requires a thorough examination of drugs using many different models and approaches, including a variety of animal species.

Face validity

Appearance of a test measuring what a researcher considers it to measure

Face validity refers to the appearance of a test measuring what a researcher considers it to measure. For example, researchers study drugs for Alzheimer's disease by testing mice with memory deficits. Memory deficits are a prominent symptom of Alzheimer's disease. Thus, testing memory in mice offers face validity for

Alzheimer's disease. Sometimes, animal models offer no face validity. In particular, testing antipsychotic drugs for treating schizophrenia, a disorder in which individuals can experience auditory hallucinations among many other symptoms, must often be tested in models lacking face validity. That is, we lack animal models for paranoia and hearing voices.

Construct validity addresses how well a study's findings relate to the underlying theory of a study's objectives. Testing new drugs for Alzheimer's disease in Alzheimer's patients offers high construct validity; that is, the drug is tested in an individual who has the disease to be treated, including all of the genetic causes of Alzheimer's disease and the resulting damage to cells in the brain. Yet, we must first screen experimental drugs in animals to ensure their safety and potential effectiveness before testing novel drugs in humans.

Testing such drugs in normal mice, which lack genetic and biological features of Alzheimer's disease, leads to construct validity concerns, because normal mice do not have any of the genetic and biological features of this disease in humans. After all, the objective for such a study would be to find the model most similar to Alzheimer's disease in order to use it for identifying potential treatments. However, researchers have developed genetically altered mice that have certain protein abnormalities similar to those found in Alzheimer's disease. Testing treatments for Alzheimer's disease in these mice provides greater construct validity than testing these treatments in normal mice.

Predictive validity addresses how well a model predicts treatment effects. To continue the preceding example, an experimental drug might improve memory in certain genetically altered mice and later prove to treat Alzheimer's disease. If this were the case, then these mice offer predictive validity for screening Alzheimer's disease medications. At times, an experimental procedure might offer high predictive validity but fail to offer face or construct validity. Many animal models for antipsychotic drugs fail to exhibit features of schizophrenia, yet antipsychotic drugs produce unique behaviors in these models that scientists have learned predict certain clinical effects in humans. Drug developers rely on models with high predictive validity when screening experimental drugs.

Construct validity

How well a study's findings relate to the underlying theory of a study's objectives

Predictive validity

How well a model predicts treatment effects

STOP & CHECK

1. How is a correlational study different from an experiment?
2. Why is external validity an important concern for animal experimentation?

1. Correlational studies identify potential associations between variables, whereas experiments identify causal relationships between variables. 2. Important physiological differences exist across all species, and these differences may not accurately reflect a drug's actions in humans.

Ethical Considerations in Research

Ethics plays another important role in psychopharmacology research. In particular, experimental treatments may cause serious adverse effects or simply be ineffective for the disorders they were developed for. Thus, participants may be exposed to a dangerous medication and, more than this, may experience no improvement in a disorder they are suffering from. Ethically, and fortunately also legally, researchers engage in years of testing and development before testing a potential treatment in humans.

To develop drugs for human usage, medical research relies heavily on animal testing. Not only do medical research advances depend on animal models, but governmental regulators, such as the FDA, also require proof of extensive animal research before approving drugs for human testing. Medical advances rely on animal research for two major reasons: a lack of feasible alternatives and the ability to predict drug effects in humans.

A Lack of Feasible Alternatives to Animals

Treatment results from studies conducted only on cells and tissues poorly predict treatment efficacy and safety in humans. Although these biological studies provide important steps in medical development, they fail to model the complexity of living organisms. This complexity currently precludes computer simulations or mathematical models from taking the place of animal research. Thus, animal models provide a necessary step in discovery and drug development.

Humans also do not provide a feasible alternative to animal models. Necessary basic research procedures consist of invasive techniques that would be highly unethical to perform in humans. For example, many medical studies require measuring drug-induced changes in cells and tissue by inserting probes into the brain. In addition to invasiveness, experimental drugs that have not been tested in animals carry a risk of severe and possibly irreversible adverse effects in humans. Animal testing prevents dangerous experimental drugs from being tested in humans.

High Predictive Value for Drug Effects in Humans

Beyond having no feasible alternatives, animal models do well in predicting drug effects in humans despite inherent challenges for external validity (see, for example, the earlier discussion about thalidomide). During drug development animal models identify effective drugs from the hundreds or thousands synthesized in a drug development program. The FDA requires that all experimental medications be screened in animal models before testing drugs in humans in order to ensure that there is a reasonable likelihood of improving a disorder in humans. For this same reason, the FDA requires screening for adverse effects in animal models, given that adverse effects occurring in animals may likely occur in humans as well. At the end of this chapter, the “From Actions to Effects” section describes the role that animals play in therapeutic drug development programs.

The Regulation of Animal Research

Governmental and private agencies exist to oversee the responsible and humane use of animal subjects for research or teaching purposes. Publishers of journals, where scientists report their studies, play a role by insisting that findings produced from animal research followed appropriate regulations and policies. In short, all legitimate journals publishing scientific studies require high ethical standards for animal care and use in research.

Two government agencies regulate academic and industrial animal research in the United States: the U.S. Department of Agriculture (USDA, 2006) and the Public Health Service (PHS, 2002). The USDA enforces regulations in the Animal Welfare Act, and the Office of Laboratory Animal Welfare enforces policies of the Public Health Service. Failure to comply with federal regulations and policies results in stiff penalties, including institutional fines and withdrawal of federal grant money.

Both the Animal Welfare Act and the Public Health Policy require that U.S. institutions have an Institutional Animal Care and Use Committee (IACUC). This requirement not only pertains to academic institutions but also to industry, such as pharmaceutical companies. The FDA will not approve any treatments resulting from animal studies that have not complied with federal regulations and policies (FDA, 2002).

The IACUC oversees an institution's entire animal care and use program, including quality of housing, veterinary practices, and research practices. All animal experiments require IACUC approval before they begin. To gain approval, researchers must submit animal research proposals to the IACUC. The IACUC then reviews these protocols and determines their abidance with federal and internal policies. Moreover, the IACUC makes ethical judgments according to the "3 Rs."

The 3 Rs stand for "replacement," "reduction," and "refinement," and serve as a basis for determining whether a researcher needs to use animals for a study, and if so, the extent and nature of this research (National Research Council, 2011; Russell & Burch, 1959). For the first R, *replacement*, the IACUC assesses the necessity of using animals for a proposed study by asking, "Can animals be replaced with something else?" Sometimes, equally useful findings may be derived by working only with cells or perhaps with invertebrates (e.g., insects) instead of using animals. An IACUC will reject animal research proposals when such feasible alternatives exist.

The second R, *reduction*, refers to using the minimum number of animals necessary to achieve the study objectives. Generally, IACUCs use statistical methods to ensure that researchers use only the minimum number of animals necessary to detect experimental results. For the third R, *refinement*, the IACUC attempts to minimize any pain and distress experienced by the study animals. These attempts may include changing experimental procedures, requiring analgesic drugs to reduce pain, or using different testing equipment.

IACUCs also weigh the proposed study's ethical costs. **Ethical cost** assessments weigh the value of potential research discoveries against the potential pain and distress experienced by research subjects (**Figure 1.5**). For example, IACUC members easily justify painless experiments in animals that aim to develop treatments for lethal illnesses. Essentially, these studies provide tremendous gains with minimal

The 3 Rs

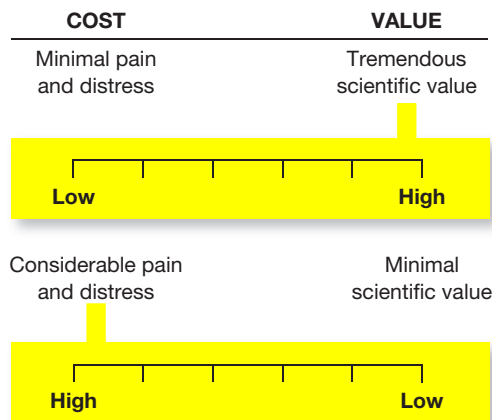
A review process for animal research that considers "replacement," "reduction," and "refinement" to determine the necessity of using animals, minimum number of animals needed, and procedures to minimize pain and distress

Ethical cost

Assessment that weighs the value of potential research discoveries against the potential pain and distress experienced by research subjects

FIGURE 1.5 Ethical Costs for Animal Research

During IACUC review, researchers weigh the potential pain or distress experienced by an animal against a study's potential value. In the top panel, the scientific value outweighs the minimal pain or distress experienced by animals, whereas the bottom panel shows that the scientific value fails to outweigh considerable pain and distress expected for the animals.



ethical cost. However, IACUC members cannot justify studies with limited potential for discovery that use highly painful procedures (Carbone, 2000).

Researchers Consider Many Ethical Issues When Conducting Human Research

Like animal studies, ethics committees review research practices in humans to ensure federal regulatory and policy compliance and to weigh the ethics of proposed human studies. Beyond the obvious species differences, human and animal research differs in the ability to provide informed consent. **Informed consent** consists of a participant's agreement to enroll in a study after having a thorough understanding of a study's procedures, possible gains, and potential risks. In other words, human participants know what they are getting into and can freely decide to enroll in the study. Animals, of course, cannot provide informed consent (Swerdlow, 2000).

However, some human participants also lack the capacity to provide informed consent. For example, young children lack the ability to understand what may happen during a medical study. Or, an adult may be mentally incapable of providing informed consent. In these cases, informed consent is left to a legal guardian.

The informed consent principle is a relatively modern one, and there is a long history of human experimentation conducted either against the will of the participants or with complete dishonesty about what was being studied. The Nuremberg Principles, which arose from the Nuremberg Trials after World War II, consist of some of the first written statements about the ethical conduct of human research.

Informed consent

Consent gained after a participant thoroughly understands a study's procedures, possible gains, and potential risks

These principles provided the foundation for the Declaration of Helsinki, another set of guidelines for ethical research using humans.

In the United States, the federal Department of Health and Human Services regulates human research. This department assigns the direct responsibility of enforcing these regulations to the Office of Protection from Research Risks. These regulations require that U.S. institutions review and approve all human research in accordance with these federal regulations. U.S. institutions must also file annual reports on human research activities. The penalties for violating government regulations and policies may range from fines to freezing an institution's federal research funding.

STOP & CHECK

1. Why are animal models valuable?
2. When evaluating animal research proposals, what considerations are made in an ethical cost assessment?
3. Aside from species differences, what is the major distinction between human research and animal research?

1. Although animal models present important experimental validity challenges, animal models remain the only feasible models because they are effective and provide ways to evaluate drugs under carefully controlled conditions. 2. By considering ethical costs, an IACUC weighs the benefits of a research proposal against the potential pain and suffering experienced by animal subjects. 3. Humans can provide informed consent whereas animals cannot.

From Actions to Effects: Therapeutic Drug Development

Academic, government, and pharmaceutical company research contributes to the development of therapeutic drugs (e.g., Blake, Barker, & Sobel, 2006). For the most part, academic and government research consists of basic research discoveries about disorders and the development of theoretical directions for designing new treatments. This work may include characterizing a disorder's effects on the nervous system or developing a theory about chemical structures that mimic chemicals in the nervous system. Although some institutions develop new treatments, the vast majority of new treatments arrive from pharmaceutical companies.

Pharmaceutical drug research and development generally occurs in several stages (Blake et al., 2006; Dingemans & Appel-Dingemans, 2007; Jenkins & Hubbard, 1991) (see **Table 1.5**). First, a company usually decides for which disorder to develop a treatment. This decision includes carefully considering opinions from scientists, outside consultants, and business executives. These individuals seek to develop a feasible treatment that yields a reasonable likelihood of making a significant profit.

TABLE 1.5 Stages of Therapeutic Drug Development

Stage	Purpose	Description
1	Identify disorder to treat	Decisions include feasibility and profitability concerns.
2	Drug synthesis	Chemists synthesize experimental compounds.
3	Biological experimentation	High-throughput screening methods provide basic biological information about compounds. Results are sent to chemists and guide synthesis of further compounds.
4	Focused screening methods	Focused testing occurs with most promising compounds identified during Stage 3.
5	Safety pharmacology	Tests identify adverse effects and toxic doses.
6	Clinical trials	Most effective and safest compounds tested from previous stages are tested in humans. Regulatory approval sought after positive clinical findings.

The likelihood of a profit coincides with a disorder’s prevalence and the amount of scientific knowledge available about a disorder. In other words, companies assess the size of the market and the likelihood that research and development efforts can use known information to successfully invent a new drug treatment. In this regard, rare and incurable diseases are often incurable because there is a small market and relatively little scientific knowledge about them. For a rare disease, there must be a high potential of developing a successful treatment, making a research and development program low risk.

Drug synthesis occurs during the second drug development stage. During this stage, a company’s chemists develop experimental compounds. To do so, they may develop variations of existing therapeutic drugs for a disorder or develop drugs based on established theories.

Third, the drugs produced by the chemists during Stage 2 are tested in biological experiments. For example, researchers may assess how well experimental drugs bind to certain proteins in tissue samples. During this stage, researchers prefer using **high-throughput screening** methods—rapid testing processes involving a large number of experimental drugs (Garrett, Walton, McDonald, Judson, & Workman, 2003; Szymański, Markowicz, & Mikiciuk-Olasik, 2012). Generally, high-throughput tests provide quick results and can determine whether the experimental drugs appear to be achieving a desired biological effect.

Chemists receive these test results and use the information to develop more experimental drugs. The most on-target drugs from the previous batch of experimental drugs serve as the best directions for synthesizing the next series of drugs. The chemists then send the newest drugs back to the high-throughput screeners. The back-and-forth continues as each new series of drugs comes closer to achieving

High-throughput screening
Rapid testing process involving a large number of experimental drugs

a particular biological effect. When a drug meets the researchers' goal for a biological effect, then drug testing moves to the next stage of development.

Stage 4 represents a shift from high-throughput screening methods to highly focused screening methods. Compared to high-throughput screening methods, these screening methods are slower, but offer greater precision about a drug's effect. In particular, researchers use models that have face, construct, or predictive validity. Often, these methods include animal models.

After drugs pass through tests in Stage 4, researchers determine a drug's adverse effects. Thus, Stage 5 consists of **safety pharmacology** testing, or screening processes that identify a drug's adverse and toxic effects (Guillon, 2010; Szymański et al., 2012). Adverse effects include mild to serious physiological effects, addiction risks, and changes in mental functioning. As noted in the chapter, we identify adverse effects too severe to warrant exposing patients to toxic effects. Safety pharmacology tests seek to identify a drug's toxic doses.

Many drugs determined successful in earlier stages of screening reveal a low therapeutic index during safety pharmacology testing—that is, the same doses that produce therapeutic effects are near those that produce toxic effects. For drugs to meet clinical testing approval from governmental regulatory agencies such as the FDA, safety pharmacology tests must demonstrate that a drug's toxic doses are much higher than its therapeutic doses.

Stage 6 of drug development involves human drug testing. Most drugs fail to make it to this stage, having been abandoned because of a lack of efficacy or poor safety. A **clinical trial** is a government-approved therapeutic drug experiment in humans. Clinical trials describe the number of treatments and doses provided to groups of study participants as **treatment arms**. For example, a two-arm design refers to two experimental groups. Often, one group of participants receives an experimental drug and the other group receives a placebo. A **clinical study report** details a clinical study's design and results (International Conference on Harmonization, 1996).

In the United States and other countries, different phases describe the progression of experimental testing throughout the clinical trial process (**Table 1.6**). Clinical trials begin at Phase 1 and progress through Phases 2 and 3 as long as a drug continues to prove safe and effective. The FDA may request a Phase 4 trial after approving a drug for market in order to further assess the efficacy and safety of the drug (National Institutes of Health, 2012).

The primary goal of a Phase 1 clinical trial is to determine a drug's safety in humans. Phase 1 clinical trials employ a low dose of drug and provide it to healthy human volunteers if feasible or to a specific patient population for a short period of time. For example, a new pain-relieving drug might first be given to healthy human volunteers, whereas a new cancer-treating drug might need to be given to cancer patients, but perhaps only to those with a specific type of cancer. Clinical investigations will not continue with the compound if it is found unsafe in Phase 1.

During Phase 2 clinical trials, researchers primarily seek to measure a drug's therapeutic efficacy by recruiting volunteers with the disorder to be treated. Phase 2 clinical trials tend to use larger doses that are administered short term, but perhaps longer than Phase 1. These trials often include for comparison an FDA-approved

Safety pharmacology

The study of a drug's adverse effects

Clinical trial

A government-approved therapeutic drug experiment in humans' drug development; a multistep process of developing an effective, safe, and profitable therapeutic drug

Treatment arms

Number of treatments and doses provided to patients described in a clinical study

Clinical study reports

Detailed summaries of a clinical study's design and results

TABLE 1.6 Clinical Trial Phases

Clinical Trial Phase	Goals	Dose and Duration of Treatment	Participants Involved
Phase 1	Determine a drug's most likely and frequent adverse effects to occur during treatment	Low dose of the drug given short term	Normally healthy volunteers if feasible
Phase 2	Determination of therapeutic effectiveness; experimental drug may be compared to standard medical treatment; adverse effects continue to be monitored	May be higher dose of drug, but still given short term	Participants with disorder to be treated
Phase 3	Further determination of therapeutic effectiveness; experimental drug may be compared to standard medical treatment; adverse effects continue to be monitored	Dose selected based on Phase 2 results, but likely given long term	Participants with disorder to be treated, but more inclusive for other populations and those with coexisting conditions
Phase 4	Occurs after FDA approves a drug for the market; might address remaining questions or concerns about the drug; goal is to further determine features of a drug's therapeutic effectiveness and adverse effects	Dose selected based on Phase 3 results, but likely given long term	Participants with disorder to be treated, might focus on unique effects in different populations or certain other medical conditions; choice of participants may come from results of Phase 3

drug that is normally considered to be a standard medical treatment for the disorder. Through using a comparison drug, drug developers determine how well their drug will compete with others on the market. A company may see no benefit to continuing clinical trials for an experimental drug found only as effective as drugs already on the market.

Phase 3 clinical trials provide greater information about the drug's therapeutic effects and potential adverse effects. These trials rely on results from Phase 2 to determine the selection of drug doses (kept the same, or adjusted higher or lower) and normally have a longer duration of drug treatment. Moreover, researchers recruit study participants to have a greater diversity of human populations and health backgrounds than those in previous trials. The FDA grants market approval to drugs deemed safe and effective after Phase 3, although the FDA may request further monitoring after the drug goes to market. Further monitoring occurs during Phase 4 clinical trials, which may be designed to address any remaining questions or concerns from earlier phases. Thus, Phase 4 trials may employ higher doses, use longer durations, or focus on some specific human population or coexisting health condition. For example, a drug for treating tobacco addiction³ might be further examined

³I refrain from using "nicotine addiction" in this book because there are other psychoactive ingredients in tobacco that make quitting hard to do.

in Phase 4 trials in those with tobacco addiction who are also clinically depressed. The approximate cost for bringing a drug through the research and development process and eventually onto the market is \$2.6 billion (Mullard, 2014).

STOP & CHECK

1. What most likely happens after the first time drugs are initially screened?
2. Why might an effective and safe drug be removed from clinical trials?

1. Usually, chemists take data from the first screened batch and make further chemical compounds. The interplay between the chemists and the high-throughput screeners continues until the best drugs are made. 2. Sometimes, drugs are removed from clinical trials because they fail to be more effective than drugs that are already on the market. A company may decide there's no profit to be made in this case.

Psychopharmacology is the study of how drugs affect mood, perception, thinking, or behavior. The field bridges psychology and pharmacology. Psychoactive drug use is highly prevalent in society. Alcohol, for example, is consumed by much of the U.S. population, and antidepressant medications are used by close to a third of the Western population. Learning about psychopharmacology provides a greater understanding of behavior and how mental disorders are treated. Defined as substances that alter physiological functioning, drugs are known by generic, brand, chemical, and street names. Drug amounts used are described as doses, and understanding drug effects and actions requires knowledge of pharmacokinetic and pharmacodynamic

actions. Moreover, genetic differences account for varying drug effects among individuals. Drugs fall into two categories: therapeutic drugs and recreational drugs. However, many drugs cross both categories, depending on their usage. Researchers study the objective and subjective effects of drugs in studies that address the importance of drawing valid inferences from study results. Drug studies often employ either animal or human subjects, in abundance with regulatory and ethical guidelines. The drug development process for inventing new drug treatments begins with the decision to pursue a disorder and then proceeds through stages, including drug synthesis, tests for efficacy and safety, and finally human clinical trials.

Psychopharmacology 2
Psychoactive drugs 2

Drug 4
Instrumental drug use 5

Psychotropic drug 5
Recreational drug use 6

Drug misuse	6	Pharmacokinetics	11	External validity	18
Brand name	6	Pharmacogenetics	11	Teratogen	18
Generic name	6	Objective effects	12	Face validity	18
Chemical name	6	Subjective effects	12	Construct validity	19
Street name	7	Dependent variable	15	Predictive validity	19
Dose	7	Independent variable	15	The 3 Rs	21
Dose-effect curve	8	Experimental study	15	Ethical cost	21
ED ₅₀ value	8	Placebo	16	Informed consent	22
Potency	9	Single-blind		High-throughput	
Therapeutic index	9	procedure	16	screening	24
Certain Safety Index	10	Double-blind procedure	16	Safety pharmacology	25
Additive drug effects	10	Open-label studies	16	Clinical trial	25
Synergistic drug effects	10	Correlational study	16	Treatment arms	25
Pharmacodynamics	11	Internal validity	18	Clinical study report	25

The Nervous System

Chapter Outline

- Cells in the Nervous System
- The Nervous System
- Cerebral Blood Flow and Cerebrospinal Fluid
- Genes and the Physiological Processes of Cells
- From Actions to Effects: Advances in Therapeutic Use of CRISPR Genetic Technology

Learning Objectives

- Explain the components and functions of cells in the nervous system
- Identify the features and functions of structures and systems in the nervous system
- Describe the function of genes and their impact on cells

The study of psychoactive drugs requires knowledge about how drugs act on the nervous system. This chapter provides a basic overview of the nervous system, with an emphasis on cells and structures important for psychoactive drug effects.

Cells in the Nervous System

Each structure of the brain contains a dense ensemble of neurons and glial cells. **Neurons** are specialized cells in the nervous system that control behavior, convey sensory information, and signal movement. Neurons communicate by receiving and transmitting information to neurons and glial cells in the nervous system via chemicals called *neurotransmitters* (covered in Chapter 3). **Glial cells** support the function of neurons. General estimates give the brain approximately 86 billion neurons and just as many non-neuronal cells, including glial cells (Herculano-Houzel, 2012).

Neurons

Specialized cells in the nervous system that control behavior, convey sensory information, and signal movement

Glial cells (or glia cells)

Cells that support the function of neurons

Neurons

Neurons comprise dense communication networks in the brain. These networks support the function of individual brain structures and facilitate communication between structures. Like other cells in the body, neurons have basic characteristics such as a membrane, nucleus, ribosomes, and an endoplasmic reticulum (**Figure 2.1**), yet they have many unique characteristics for cellular communication.

Neurons have four major components: a soma, dendrites, axon, and axon terminal (**Figure 2.2**). The soma is the body of the neuron. It also contains the nucleus, which holds DNA. Overall, components within the soma support a neuron's basic physiological processes.

FIGURE 2.1 Soma of a Neuron

The soma of a neuron contains the same basic components that other cells of the body have.

