Introduction to Psychopharmacology

CHAPTER OUTLINE

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• Drugs: Administered Substances That Alter Physiological Functions
• Psychoactive Drugs: Described by Manner of Use
• Generic Names, Trade Names, Chemical Names, and Street Names for Drugs
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• Chapter Summary

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. As students, scholars, practitioners, and everyday consumers, we may find that learning about psychoactive substances can be invaluable. The chapters in this book provide a thorough overview of the major classes of psychoactive drugs, including their actions in the body and their effects on behavior.
Psychopharmacology

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 brain cells and structures. Second, it covers the basic principles of pharmacology. A psychopharmacologist must also characterize the effects of different types of drugs. We cover this after learning about the basic principles of pharmacology by considering the many different types of psychoactive drugs, beginning with recreational and abused drugs such as cocaine, marijuana, and LSD and ending with therapeutic drugs for treating mental disorders such as depression, anxiety, and schizophrenia.

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>
<thead>
<tr>
<th>Field</th>
<th>Description</th>
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<tbody>
<tr>
<td>Psychopharmacology</td>
<td>The study of how drugs affect mood, perception, thinking, or behavior.</td>
</tr>
<tr>
<td>Behavioral pharmacology</td>
<td>The study of how drugs affect behavior. Sometimes behavioral pharmacologists emphasize principles used in field of behavior analysis.</td>
</tr>
<tr>
<td>Neuropsychopharmacology</td>
<td>The study of how drugs affect the nervous system and how these nervous system changes alter behavior.</td>
</tr>
</tbody>
</table>

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Why Read a Book on Psychopharmacology?

Beyond being required reading for a course you’re taking, psychopharmacology is an important part of modern psychology. First, psychoactive drug use is highly prevalent.

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In the United States, for example, consider the following:

- More than 100 million antidepressant drug prescriptions are written every year.
- More than 80 million anti-anxiety (i.e., anxiolytic), sedative, and hypnotic drugs are prescribed every year.
- More than 200 million pain-relieving drug prescriptions are written every year [Centers for Disease Control and Prevention (CDC), 2008].

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

- More than 114 million adults consume alcohol on a regular basis (CDC, 2011).
- More than 25 million individuals use marijuana.
- More than 15 million individuals misuse a prescription drug.
- More than 70 million individuals use tobacco products (Substance Abuse and Mental Health Services Administration, 2010).

The World Health Organization (WHO) also reports high rates of psychoactive drug use internationally (WHO, 2012). For us, as students, teachers, researchers, and practitioners in psychology, 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 nearly all 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. 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 develop psychoactive treatments for psychological disorders. As described later in this chapter, drugs used for treating disorders—referred to as pharmacotherapeutics—are not derived only from chemists. Rather, scientists trained in psychology test psychoactive drugs and determine their potential effectiveness for psychological disorders.

**Drugs: Administered Substances That Alter Physiological Functions**

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 depression or anxiety, and drugs for virtually any other ailment or disorder. We even take drugs to prevent disorders. But what exactly is a drug?

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 exhibit sufficient efficacy to change physiological processes.
This definition has challenges. The term *administered* excludes substances made naturally in the body. For example, 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.

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**FIGURE 1.1**  
(a) Antidepressants (b) Vitamins (c) Vaping (d) Sniffing glue

SOURCE: Clockwise from top left: Copyright iStock Photo/svetikd; Copyright gosphotodesign/Shutterstock.com; Copyright iStock Photo/diego_cervo; Copyright Jan H Andersen/Shutterstock.com.
The term *substance* in the definition of drug also lacks a precise description. The antidepressant in panel A clearly seems to be 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. Some teenagers 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. How prevalent is psychoactive drug use?
2. What is the definition of a drug?

*Psychoactive Drugs: 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 **therapeutic drugs**—drugs used for treating disorders—for treating mental disorders such as depression and schizophrenia.

**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. Of course, we might describe alcohol use as instrumental if a person were only using it for another purpose such as relieving stress after a long day of work. Again, the intended use distinguishes instrumental use from recreational use. The term *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 Names, Trade Names, Chemical Names, 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 *trade name* and acetaminophen as its *generic name*.

Nearly all therapeutic drugs have a generic name and at least one trade name. A pharmaceutical company that develops and markets a drug provides both trade and generic names, each for different purposes. A drug’s *trade name* (or *brand 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 names of the following antipsychotic drugs: chlorpromazine, clozapine, and olanzapine. All three of these drugs end in *-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 trade name in parentheses. Moreover, trade names are capitalized. For example, a report might read “Physicians prescribe zolpidem (Ambien) for insomnia.” The generic name is zolpidem, and its trade 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 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 also reflect the drug’s effects. For example, the drug MDMA is also known as **ecstasy**, which describes the drug’s pleasurable effects. **Table 1.2** lists common recreational substances and their popular street names.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Street Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines</td>
<td>Bennies, black beauties</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Candy, downers, sleeping pills</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Coke, rock, crack</td>
</tr>
<tr>
<td>Dextromethorphan (used in cough syrup)</td>
<td>Robo, triple C</td>
</tr>
<tr>
<td>Marijuana</td>
<td>Joint, blunt, weed</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>Meth, ice, crystal</td>
</tr>
<tr>
<td>MDMA</td>
<td>Ecstasy, Adam</td>
</tr>
<tr>
<td>LSD</td>
<td>Acid, blotter</td>
</tr>
<tr>
<td>Phencyclidine</td>
<td>PCP, angel dust</td>
</tr>
</tbody>
</table>

**TABLE 1.2** Street Names for Selected Drugs


**Drug Effects: Determined by Dose**

Drug effects depend on the dose of a drug. **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, 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 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 a 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 ED$^{50}$ value. An ED$^{50}$ value represents the dose at which 50 percent of an effect was observed. The "ED" stands for "effective dose."

As shown in Figure 1.2, drug A's ED$^{50}$ value 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 ED$^{75}$ (i.e., dose at which 75 percent of the effect was observed) or ED$^{15}$ (i.e., dose at which 15 percent of the effect was observed), value 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$^{50}$ values 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.

Consider again the drugs in Figure 1.2. Drug A produces the same degree 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$^{50}$ value allows us to calculate the relative level of potency between different drugs. Drug A has an ED$^{50}$ value of 4.0 mg/kg, and drug B has an ED$^{50}$ value of 10.0 mg/kg. The potency difference is calculated from dividing drug B, the compound with the highest ED$^{50}$ value, by drug A, the compound with the lowest ED$^{50}$ value. 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$^{50}$ value (TD stands for toxic dose). In this case, we interpret a TD$^{50}$ value as the dose at which 50 percent of the subjects had the particular adverse 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 a 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$^{50}$ value by an ED$^{50}$ value. A therapeutic index answers this question: How different is a dose that

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1 Alternatively, an ED$^{50}$ value can reflect a dose at which 50 percent of the subjects exhibited a full effect.
causes toxic effects in half of the subjects from a dose of the same drug that produces therapeutic effects in half of the subjects?

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 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$_{1}$—and divide this 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.

**Figure 1.3** 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$_{50}$ value (TD$_{50}$ = 6.0 mg/kg) is three times greater than the ED$_{50}$ value (ED$_{50}$ = 2.0 mg/kg). Yet notice that at the ED$_{50}$ dose (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.
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 life-threatening adverse 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?

**Pharmacology: Pharmacodynamics, Pharmacokinetics, and Pharmacogenetics**

Pharmacodynamics and pharmacokinetics represent two major areas in pharmacology. **Pharmacodynamics** refer to the physiological 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.

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 physicians to alter treatment plans. 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.

**Psychoactive Drugs: Objective and Subjective Effects**

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 increase heart rate. A researcher can objectively measure an individual’s heart rate by taking the person’s pulse (Figure 1.4).

![Figure 1.4](image)

**FIGURE 1.4** 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.

Her pulse is 105 beats per minute.

Rate from strongly disagree to strongly agree: I feel “on edge” after taking this drug.

SOURCE: Left: Copyright iStock Photo/kali9. Right: Copyright iStock Photo/dima_sidelnikov.
Subjective effects are pharmacological effects that cannot be directly observed by others. In other words, we cannot observe or measure another’s drug experience. Researchers measure subjective effects by asking study participants to describe a drug’s effects as well as using rating scales, such as the Profile of Mood States Questionnaire (POMS). The POMS asks participants to rate the degree of agreement with a word or statement that describes how they might feel, such as “energetic” or “on edge,” with rating options ranging from “a little” to “extremely” (McNair, Lorr, & Droppleman, 1971). 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.

Despite some scientific limitations, a psychoactive drug’s subjective effects are more important to understand 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?

Subjective effects are pharmacological effects that cannot be directly observed by others.

**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.
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.

Research studies fall into two categories: correlational studies and experimental studies (see Table 1.3). In a **correlational study**, an investigator does not alter the independent variable. 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.

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Description</th>
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<tbody>
<tr>
<td>Correlational study</td>
<td>No alteration of study conditions. Changes in study variables are observed, and relationships are inferred.</td>
</tr>
<tr>
<td>Experimental study</td>
<td>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.</td>
</tr>
</tbody>
</table>

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 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.

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

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**TABLE 1.3 Correlational and Experimental Studies**

**Independent variable** Study conditions or treatments that may affect a dependent variable

**Correlational study** Study in which an investigator does not alter the independent variable

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

**Placebo** Substance identical in appearance to a drug but physiologically inert
Experiments such as these indicate that the independent variable caused changes to the dependent variable.

Clinical drug studies use other terminology to describe an experiment. Drug experiments in clinical trials describe the number of treatments and doses provided to groups of study participants as treatment arms. 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.

Many times, researchers require more than a dose-versus-placebo comparison. In these cases, researchers may use more arms in a study design. For example, a three-arm design may consist of a high-dose drug group, a low-dose drug group, and a placebo group. Or a treatment arm may include an entirely different drug. Testing an experimental drug in comparison with a standard treatment and placebo provides a valuable assessment of drug efficacy compared to existing medications or no medications, respectively.

Why are study groups called arms? Look at the examples of two-arm and three-arm designs in Figure 1.5. This is the standard style of illustrating multiple group

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**FIGURE 1.5** - Clinical drug study designs describe treatment conditions as arms. In these examples, the left portion of each design shows the total number of participants recruited for the study, and each arm shows the number of participants assigned to each study condition.
study designs in **clinical study reports**, the detailed summaries of a clinical study’s design and results (International Conference on Harmonization, 1996). As shown in Figure 1.5, the different groups appear on separate lines like arms or branches.

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.

**Validity: Addressing the Quality and Impact of a Study**

Say you conducted an experiment and found that a newly developed drug reduced symptoms in depression. Great news, but how good was the experiment? 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 include internal validity, external validity, face validity, construct validity, and predictive validity (**Table 1.4**).

**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 be sufficient to reduce depression 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 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. 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 exhibited sedative effects and prevented nausea and vomiting. Without harmful effects to fetuses in pregnant mice, European physicians prescribed thalidomide to pregnant women suffering from morning sickness.

However, thalidomide proved severely harmful to human fetuses. By 1962, nearly 10,000 babies had been born with missing fingers, toes, and limbs after exposure to thalidomide during pregnancy (Figure 1.6). In humans, but not in mice, thalidomide was metabolically transformed into a **teratogen**, a substance harmful to a fetus. Had drug developers tested thalidomide in rabbits, which do convert thalidomide into this teratogen, doctors would not have prescribed thalidomide.

<table>
<thead>
<tr>
<th>Validity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal validity</td>
<td>Adequacy of controlling variables that may influence a dependent variable</td>
</tr>
<tr>
<td>External validity</td>
<td>Ability to extend findings beyond study conditions</td>
</tr>
<tr>
<td>Face validity</td>
<td>Test appears to measure what a researcher considers it to measure.</td>
</tr>
<tr>
<td>Construct validity</td>
<td>How well a study’s findings relate to the underlying theory of a study’s objectives</td>
</tr>
<tr>
<td>Predictive validity</td>
<td>Ability of model to predict treatment effects</td>
</tr>
</tbody>
</table>
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** 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

---

**FIGURE 1.6** Failure to screen thalidomide in rabbits instead of mice led researchers to miss thalidomide’s teratogenic effects, leading to babies born with missing digits and limbs.

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**SOURCE:** Photo by Leonard Mccombe/The LIFE Picture Collection/Getty Images.
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 risking testing these 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 theoretical 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 predicts certain clinical effects in humans. Drug developers rely on models with high predictive validity when screening experimental drugs.

**STOP & CHECK**

1. How is a correlational study different from an experiment?
2. What might a three-arm clinical study consist of?
3. Why is external validity an important concern for animal experimentation?

**Animals and Advancing Medical 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 is 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**

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. 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**

In developed nations, governmental and private agencies exist to oversee the responsible and humane use of animal subjects for research or teaching purposes. Publishers of journals, in which scientists publish reports of their studies, indirectly regulate non-participating countries by insisting that all research described in their journals abide by certain 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.

Among the many rules of institutional conduct, both the Animal Welfare Act and the Public Health Policy require that all U.S. institutions conducting federally funded animals research establish an ethics review committee called the Institutional Animal Care and Use Committee (IACUC). The Animal Welfare Act also covers many species regardless of an institution’s federal funding status. Federal law not only pertains to academic institutions but also to 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, provides a means for refining a study’s plan to use animals (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 alternatives exist.

The second R, reduction, refers to using the minimum number of animals necessary to achieve the study objectives. Generally, IACUCs use statistics 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 animals (Figure 1.7). 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 ethical cost. However, IACUC members cannot justify studies with limited potential for discovery that uses highly painful procedures (Carbone, 2000).

During IACUC review, researchers weigh the potential pain or distress experienced by an animal against a study’s potential value. In the top panel of Figure 1.7, 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.
Beyond federally mandated regulations and policies, many U.S. institutions seek private accreditation in order to exceed federal requirements and achieve best practices in the animal care and use. The primary private accreditor for animal care and use in research settings is the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC). AAALAC inspection teams tour animal facilities, talk to researchers, and oversee how animal research is approved and monitored. AAALAC is an important aid to larger institutions that use thousands of animals for research (AAALAC, 2012).

Animal Rights Activism Seeks to Eliminate Animal Research

The previous section provides information about the use of animals in research and the ethical policies and legal regulations overseeing the humane use of laboratory animals. Animal rights groups such as the People for the Ethical Treatment of Animals (PETA) and the Animal Liberation Front (ALF) have a general goal of actively seeking the complete cessation of animal research, either seeing no value in the work or dismissing any value as ethically unjustified.

Historically, animal rights groups arose from concerns over animal vivisection, a procedure involving surgical procedures on living, and often awake, animals. These concerned individuals formed antivivisection societies in the late nineteenth century, and their efforts led to the Cruelty to Animals Act of 1876 in Great Britain. This act forbade painful procedures in animals unless “absolutely necessary for the due instruction of the persons to save or prolong human life.”

In the United States, animal rights groups formed by concerned citizens, including many animal researchers, fought unsuccessfully for national animal research regulations. But the situation changed in the 1960s. In 1966, a Life magazine article exposed unethical activities of some animal research dealers, including catching stray dogs or even stealing dogs for the purpose of selling them to animal researchers. An outraged
public quickly led federal legislators to pass the Animal Welfare Act in 1966. Among other regulations, the Animal Welfare Act required researchers to obtain animals from federally approved animal dealers.

Modern animal rights activities largely began after publication of philosopher Peter Singer’s book *Animal Liberation* (Singer, 1975). Today’s animal rights groups are active and well supported. Most take legal actions, but some take illegal actions against animal research.

Legal animal rights activities may include information sessions, public protests, petitions, and advertising. Illegally animal rights activities include distributing false information, illegally entering animal facilities, releasing laboratory animals, and damaging laboratory equipment. Recent years have seen terrorist activities directed

**FIGURE 1.8** Since 1997, illegal animal rights activist activities have occurred in most American states. States colored dark blue in this map have had a high number of incidents, whereas light blue-colored states have had a low number of incidents. Gray indicates no reported incidents.

![Map of United States showing number of animal rights incidents](source: Image provided by the Foundation for Biomedical Research.)
at animal researchers ranging from acts of vandalism to attempted murder. A string of incidents of vandalism and fire bombings of vehicles and homes has been linked especially to the ALF over many years (Lewis, 2005). In response to growing threats to researchers and students, groups supporting animal research publicize information on animal research medical discoveries. The Foundation for Biomedical Research, for example, informs the public about illegal animal rights activities (Figure 1.8) and produces media describing medical advances from animal research.

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 according 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. 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 range from fines to freezing an institution’s federal funding.

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; Dingemanse & Appel-Dingemanse, 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

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

Feasibility and profitability often steer a research program into conservative directions, where instead of attempting treatments for currently incurable diseases, companies seek to improve treatments for currently treatable disorders. In fact, many new drugs are derived from active ingredients in natural products (Patridge, Gareiss, Kinch, & Hoyer, 2016). For example, the cough suppressant codeine is an active compound in opium, which is exuded from poppy plants. But occasionally companies will seek a high-risk, high-reward approach. For example, developing a cure for cancer or acquired immunodeficiency syndrome (AIDS) seems an insurmountable challenge, but the profit gained from such a treatment would be tremendous.

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 further 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 drug comes closer to achieving 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, 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. 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).

### Table 1.6 Clinical Trial Phases

<table>
<thead>
<tr>
<th>Clinical Trial Phase</th>
<th>Goals</th>
<th>Dose and Duration of Treatment</th>
<th>Participants Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>Determine a drug’s most likely and frequent adverse effects to occur during treatment</td>
<td>Low dose of the drug given short term</td>
<td>Normally healthy volunteers if feasible</td>
</tr>
<tr>
<td>Phase 2</td>
<td>Determination of therapeutic effectiveness; experimental drug may be compared to standard medical treatment; adverse effects continue to be monitored</td>
<td>May be higher dose of drug, but still given short term.</td>
<td>Participants with disorder to be treated</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Further determination of therapeutic effectiveness; experimental drug may be compared to standard medical treatment; adverse effects continue to be monitored</td>
<td>Dose selected based on Phase 2 results, but likely given long term</td>
<td>Participants with disorder to be treated, but more inclusive for other populations and those with coexisting conditions</td>
</tr>
<tr>
<td>Phase 4</td>
<td>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.</td>
<td>Dose selected based on Phase 3 results, but likely given long term</td>
<td>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</td>
</tr>
</tbody>
</table>

*SOURCE: www.clinicaltrials.gov.*
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 trials are terminated for drugs 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 for short term, but perhaps longer than Phase 1. These trials often include for comparison an FDA-approved 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 dose (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 addiction 1 might be further examined in Phase 4 trials in those with tobacco addiction 1 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 I refrain from using “nicotine addiction” in this book, because there are other psychoactive ingredients in tobacco that make quitting hard to do.
Chapter Summary

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 the 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 names, trade names, 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. Drugs come from three different sources: plants, industry, and clandestine laboratories. 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 abidance 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.

Key Terms

Psychopharmacology 2  
Psychoactive drugs 2  
Pharmacotherapeutics 3  
Drug 3  
Instrumental drug use 5  
Therapeutic drug 6  
Recreational drug use 6  
Trade name 6  
Generic name 6  
Chemical name 7  
Street name 7  
Dose 7  
Dose-effect curve 8  
ED₅₀ value 9  
Potency 9  
Therapeutic index 9  
Certain Safety Index 10  
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