EIGHTH EDITION

Drugs and Behavior

An Introduction to Behavioral Pharmacology

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Pearson

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Eighth Edition

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Preface

Like most modern scientific endeavors, the field of behavioral pharmacology is ever changing. Each day brings exciting new developments and insights, and a great many discoveries have been made since the 1st edition of this text in 1987. These discoveries intrigue people who use drugs both therapeutically and recreationally. It is an ongoing challenge to keep current with these new developments and decide what to include in each succeeding edition. At the same time, we believe that it is important to tell the stories of the pioneers, to describe their groundbreaking research and insights, and to provide the context in which these new discoveries are made. In addition, new drugs and new trends in drug use, both recreational and medicinal, come on the scene as others wane. As students ask new and different types of questions, it is important to be able to provide well-informed answers. While every edition of this text has attempted to keep up with these rapid changes, it is sometimes difficult to keep pace, and any publication is apt to be a bit behind the times. As such, we encourage course instructors to supplement the text content with up-to-date material on new trends and developments, with the text providing background in which the significance of new developments can be understood.

New to This Edition

The 8th edition of *Drugs and Behavior: An Introduction to Behavioral Pharmacology* has been substantially revised and updated to include the newest research findings and real-world examples related to drug use and addiction. New material you will find in this edition includes:

- Updated prevalence of use data, recent trends in drug availability, and inclusion of newly revised key features (DSM-5 diagnostic criteria) of substance-related and addictive disorders (including gambling disorder), anxiety disorders, schizophrenia spectrum and other psychotic disorders, and major depressive disorder.
- The addition of pharmacokinetic, neuropharmacological, physiological, and behavioral research findings related to caffeinated alcoholic beverages, e-cigarettes, dissolvable tobacco products, energy drinks and shots, synthetic cathinones ("bath salts"), synthocannabinoids ("herbal incense"), MDMA ("ecstasy"/"molly"), and ayahuasca.
- A thoroughly emended and elaborated chapter on cannabis, rewritten to include changes in the use and composition of cannabis and cannabinoid compounds, new research evidence of drug effects, and recent legislative changes. The chapter now also contains extensive discussion of synthocannabinoids ("synthetic marijuana" or "herbal incense")—their history of emergence onto drug markets, legislation enacted to curb their distribution and use, pharmacokinetic and neuropharmacological effects, influence on human and animal behavior, and the physiological and harmful effects of these compounds.
- New chapter boxes highlighting important drug-related processes, such as pharmaceutical drug development and the classification of controlled substances, as well as contemporary issues, such as the shift in conceptualizing addiction to include behaviors such as gambling and the physical and cognitive consequences of adding caffeine to alcohol.
- An entirely new test bank collection created to help instructors assess student comprehension of the material. Each chapter of the book is now accompanied by a brief topic overview, 50 multiple-choice questions, 15 short-answer questions, and 5 essay questions.
- A change in the order of authorship. Dr. William McKim has graciously passed the reins of first authorship to Dr. Stephanie Hancock. Bill first put pen to paper to create this textbook in the early 1980s when, through his own teaching, he realized that a comprehensive text on behavioral pharmacology did not exist. Since then, he has lovingly and meticulously updated each of the previous editions, and his personable style and enthusiastic approach will continue to characterize each new edition.

Available Instructor Resources

The following instructor resources are available for download at http://www.pearsonhighered.com/irc. Login is required.

Test Bank. The book's test bank has been substantially rewritten and updated in accordance with the wealth of new information contained in the 8th edition. For each of the 15 chapters included in the new edition, a chapter overview, summary notes, 50 multiple choice questions, 15 short answer questions, and 5 essay questions have been provided to aid in assessing student learning and comprehension of the chapter material. Test questions are

arranged in the same order as material provided in each chapter, and accompanying each question is information indicating the correct answer and the section of the chapter in which it is located. In addition, each question is categorized according to the learning objective it satisfies and tagged with information regarding its level of difficulty and the degree of synthesis required to choose the correct answer.

PowerPoint Presentation. The PowerPoint Presentation is an interactive tool for use in the classroom. Each chapter pairs key concepts with images from the textbook to reinforce student learning.

Acknowledgments

This text would not have been possible without the assistance of many people. These include all the individuals acknowledged in the earlier editions whose contributions are still reflected in these pages. In this edition, we would like to further acknowledge the help of our spouses, Darron Kelly and Edna McKim, who tolerated our frequent and prolonged absences, both physical and mental, while the manuscript was being revised. Darron spent untold hours poring over chapter revisions, making corrections and suggesting improvements for the 8th edition. For this, I (S.H.) am extremely grateful.

We would also like to acknowledge the contribution of many of our colleagues at Memorial University and at other institutions around the world who have made helpful suggestions, read drafts, and corrected our errors. We also want to acknowledge the many students who have used earlier editions and contributed helpful suggestions and criticisms that have shaped this most recent edition. Thanks as well to the staff at Pearson for their commitment to this project.

Apart from taking credit where it is due, none of these people can be held responsible for errors or omissions in the text. Please direct all suggestions to us so we can make the 9th edition even better.

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About the Authors

Stephanie D. Hancock holds a Doctorate in Experimental Psychology with a focus in Behavioral Neuroscience. She is a seasoned lecturer, having taught a wide range of psychology courses, from introductory classes on general themes, to topic-specific courses on drugs and behavior, biopsychology, abnormal psychology, social psychology, educational psychology, and upper-level classes in research methods and statistics. Stephanie's research interests include drug and behavioral addictions; psychological disorders, especially stress-related and eating disorders; and the impact of early-life experiences on the development of psychopathologies. She collaborates with neuroscientists, psychologists, social workers, educators, and pharmacists on a variety of research projects, some involving laboratory animals and others involving people.

Stephanie grew up in Labrador, Canada, where her natural curiosity and independent spirit were nurtured in one of North America's last truly wild places. She currently resides in St. John's, Newfoundland, where she conducts research in the School of Pharmacy at Memorial University. Stephanie has a deep appreciation for rats, loves the British spelling of "behaviour," and greatly values the capacity of red wine and dark chocolate to hijack the brain's reward system. She is eternally grateful for the guidance and encouragement of her colleagues (Bill McKim among them), and for the love and support of her family.

William (Bill) A. McKim attended Memorial University of Newfoundland as an undergraduate and pursued graduate studies at the University of Toronto and the University of Western Ontario where he earned Ph.D. in Psychology. He spent his career at Memorial University of Newfoundland where he studied the effects of drugs on the behavior of rats and mice. During this time, he spent a sabbatical in the lab of Peter Dews at Harvard Medical School, which he found to be a transforming experience. Later, he developed an interest in the application of operant behavioral principles and the neuroscience of motivation to the understanding human drug use and abuse.

At Memorial University, Bill developed a course in Behavioral Pharmacology which he taught for 37 years. He believed that you could never really understand something until you had taught it to someone else. In the 1980s, he published the 1st edition of *Drugs and Behavior: An Introduction to Behavioral Pharmacology* and continued to update the text through many subsequent editions. He enlisted the help of Stephanie Hancock when she was a graduate student and the collaboration was so successful that she went on to be a co-author of the 7th edition, and is now senior author of the 8th edition. Bill retired from teaching in 2009 and is currently a Research Professor in Psychology at Memorial University. He lives in Ontario and spends his spare time messing around with guitar, banjo, and concertina.

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Chapter 1
Some Basic Pharmacology

1.1: What Is a Drug?

Most people understand what is meant by the term *drug*. Even so, providing a precise definition of this term is surprisingly difficult. Traditionally, a drug is defined as any substance that alters the physiology of the body. Although food and nutrients alter the physiology of the body, we do not usually think of these as drugs. Consequently, a drug is sometimes defined as a substance that alters the physiology of the body but is not a food or nutrient. While this narrower definition is often sufficient, it still lacks a sense of accuracy in capturing a universal meaning of the term drug (and highlights just how difficult it can be to formulate an exact definition for all cases).

One factor that complicates our ability to define a drug is the intention of the user. If a substance is consumed *recreationally* to get "high," or as a *pharmaceutical* to treat a disorder or medical condition, it is commonly thought of as a drug. But if that same substance is consumed accidentally or for taste or sustenance, it may not be useful to think of it as a drug. For instance, vitamin C alters physiology but is it a drug? If consumed in the form of an orange, it is clearly food, but if taken as a tablet to prevent or treat a cold, it could be thought of as a drug. A similar debate has also been waged about caffeine. As you will learn in Chapter 9, caffeine alters human physiology, but it is also used as a flavoring agent in products such as soft drinks. If consumers prefer a soft drink that contains caffeine because they like the drink's taste, perhaps caffeine should not be thought of as a drug in that instance. If the soft drink is consumed as a means of stimulating wakefulness and energy, then in that context it is appropriate to think of caffeine as a drug. Substances that impact the nervous system to alter a person's mood, perceptions, or level of consciousness (as caffeine does) are often referred to as *psychoactive* drugs. Likewise, some substances that alter the physiology of the body may best be thought of as toxins or poisons rather than as drugs. Gasoline and solvent vapors are examples. If they are *huffed* (inhaled deliberately to get high) they may be thought of as drugs. When inhaled unintentionally in the workplace, however, they may be identified as environmental toxins.

Fortunately, it is not necessary for us to form an absolute definition of the term *drug*—intuitive and working definitions will serve our purposes. However, we should never lose sight of the fact that any one definition may not be appropriate in all circumstances.

1.2: Naming Drugs

One source of confusion when learning about drugs is their myriad of names. Pharmaceutical drugs have at least three names—a chemical name, a generic name, and a trade name—and it may not always be apparent which name is being used at any given time. In addition, when used recreationally, these drugs have an assortment of street names that vary across time and place.

1.2.1: Chemical Name

All drugs have a *chemical name* stated in formal, technical jargon such as this:

> 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

A chemist can tell what the drug molecule looks like by its name. The chemical terminology, letters, and numbers indicate the drug's composition and refer to places where different parts of the drug molecule are joined. To make things more complicated, there are different conventions for numbering these parts of molecules. As a result, the same drug will have different chemical names if different conventions are used.

1.2.2: Generic Name

When a drug becomes established, its chemical name is too clumsy to be useful and a new, shorter *generic name* or *nonproprietary name* is created. The generic name for the drug whose chemical name we just struggled through is *diazepam*, an anxiety-reducing medication you will learn more about in Chapter 7. The conventions for making up generic names are handy to know because they are clues to the nature of the drug. Initially, the generic name was derived by combining parts of the chemical name, and these names are still in use.

More recently, a system has been adopted that uses a *stem* to indicate the class or function of the drug. The stem is usually the last part of the generic name, although it could be at the beginning or in the middle. For example, *oxetine* is a stem that indicates an antidepressant drug. Thus, if you see the name *fluoxetine* or *duloxetine*, you know what type of drug it is, even though you may never have heard of it before. Table 1-1 shows stems for some behaviorally active drugs.

Generic names are established in the United States by the United States Adopted Names Council (USANC) and are called United States Adopted Names (USAN). Similarly, British Approved Names (BAN) are established by the British Pharmacopoeia. Internationally, the World Health Organization establishes International Nonproprietary Names (INN). Despite attempts to harmonize the creation and adoption of generic names throughout the world, there are still cases where different names are used for the same drug. For example, the USAN *amphetamine* is still widely used in Britain and the United States, but many other parts of the world are now using *amfetamine*, the INN. Most scientific journals and textbooks published in North America (including this book) use USANC generic names.

Because establishing a generic name is a costly and time-consuming process, newly discovered drugs may be investigated extensively before generic names are officially awarded by the official naming agencies. But instead of using their clumsy chemical names, these drugs are sometimes referred to by an unofficial generic name—a code using letters and numbers established by the company. For example, you may see a name like *SKF 10,047*. The letters refer to the drug company (in this case, Smith, Kline, and French), and the numbers are a unique code for the drug. SKF 10,047 has now been assigned the generic name *alazocine*.

1.2.3: Trade Name

Drug research and development is a lengthy and costly process for pharmaceutical companies (Box 1-1 describes the rigorous, standard process of psychotherapeutic

Table 1-1 Generic Name Stems of Behaviorally Active Drugs

Generic Drug Name Stem	Definition	Examples
-azenil	Benzodiazepine receptor agonists/antagonists	bret***azenil***; flum***azenil***
-azepam	Antianxiety agents (diazepam type)	lor***azepam***
-barb-; -barb	Barbituric acid derivatives	pheno***barb***ital; seco***barb***ital; etero***barb***
-caine	Local anaesthetics	dibu***caine***
-clidine	Muscarinic agonist (various indications)	veda***clidine***; talsa***clidine***
-clone	Hypnotics/tranquilizers (zopiclone type)	pago***clone***
-dopa	Dopamine receptor agonists	levo***dopa***
-erg-	Ergot alkaloid derivatives	p***erg***olide
-eridine	Analgesics (meperidine type)	anil***eridine***
-fentanil	Narcotic analgesics (fentanyl derivatives)	al***fentanil***; mir***fentanil***; bri***fentanil***
-fylline	Theophylline derivatives	enpro***fylline***; bami***fylline***; cipam***fylline***
-giline	MAO inhibitors, type B	***s***ele***giline***
nab-; -nab-	Cannabinol derivatives	***nab***azenil; dro***nab***inol
nal-	Narcotic agonists/antagonists (normorphine type)	***nal***mefene
-nicline	Nicotinic acetylcholine receptor partial agonists/agonists	alti***nicline***
-orphan	Narcotic antagonists/agonists dextro-(morphinan derivatives)	meth***orphan***; dextr***orphan***
-oxetine	Antidepressants (fluoxetine type)	dap***oxetine***; sepr***oxetine***
-peridol	Antipsychotics (haloperidol type)	halo***peridol***
-peridone	Antipsychotics (risperidone type)	ris***peridone***; ilo***peridone***; oca***peridone***
-pidem	Hypnotics/sedatives (zolpidem type)	zol***pidem***; al***pidem***
-plon	Nonbenzodiazepine anxiolytics, sedatives, hypnotics	ocina***plon***; zale***plon***
-pramine	Antidepressants (imipramine type)	lofe***pramine***
-spirone	Anxiolytics (buspirone type)	zalo***spirone***; tio***spirone***
-stigmine	Cholinesterase inhibitors (physostigmine type)	quilo***stigmine***; teser***stigmine***
-tidine	H2-receptor antagonists (cimetidine type)	lupi***tidine***; rani***tidine***; done***tidine***
-triptyline	Antidepressants (dibenzo[a,d]cycloheptane derivatives)	ami***triptyline***

Prefixes are shown as "stem-," middle syllable as "-stem-," and suffixes as "-stem."

SOURCE: Adapted from United States National Library of Medicine, National Institutes of Health (2015), http://druginfo.nlm.nih.gov/drugportal/jsp/drugportal/DrugNameGenericStems.jsp, accessed June 30, 2015.

BOX 1-1

The Process of Pharmaceutical Drug Development

Preclinical Testing

When a new chemical entity is discovered or synthesized by researchers, it must be tested extensively before it can be developed into a useful drug. The chemical's composition, stability, solubility, toxicity, safety, pharmacokinetics, and formulation must be determined. Some of this research is conducted *in vitro* (in cells in a test tube or culture dish) and some *in vivo* (in experimental animals, usually rats or mice). If the research results show promise, a report and request to conduct further studies is submitted to the country's drug licensing authority (in the United States, an Investigational New Drug application is made to the U.S. Federal Drug Administration [FDA]; in Canada, a Clinical Trial application is submitted to Health Canada; and in Europe, a Clinical Trial Authorization Application is assessed by the European Medicines Agency [EMA]). If the application is approved, testing can proceed to clinical trials involving humans. The preclinical testing phase of drug development lasts, on average, 5 to 6 years at a cost upwards of hundreds of millions of dollars and with an estimated success rate of about 0.05% to 0.2% of chemicals tested.

Clinical Testing

Clinical tests on humans are conducted in phases over a number of years and with increasingly large samples of individuals. Phases I and II each last, on average, 2 years at costs upwards of tens of millions of dollars. Phases III and IV last, on average, 2–4 and 15 years, respectively, at costs of hundreds of millions of dollars. Only a fraction of chemicals tested at each Phase will, based on outcome, proceed to the next.

Phase I: Pharmacokinetic and Safety Testing. Between 20 and 100 healthy volunteers are paid to participate in determining the investigational drug's absorption, distribution, metabolism, and elimination from the body, as well as its dosing ranges, side effects, and safety.

Phase II: Small-Scale Effectiveness Testing. Between 100 and 300 patient volunteers participate in a closely supervised examination of the investigational drug's effectiveness and possible adverse effects.

Phase III: Large-Scale Effectiveness Testing. Clinical trials are expanded to include between 1,000 and 3,000 patient volunteers who help researchers determine drug efficacy, safety, and any adverse outcomes resulting from longer-term drug use. This testing is often carried out in university-teaching hospitals using the three-groups design described in Chapter 2. With promising outcomes, a New Drug Application or Marketing Authorization Application is filed with the country's drug licensing authority. If approved, this allows for widespread sale of the drug under its newly created trade name.

Phase IV: Postmarketing Studies. The new drug is available for prescription to any individual who might benefit from it. The pharmaceutical company must continue postmarketing surveillance of users and report to the country's licensing authority on the drug's safety, efficacy, and manufacturing processes.

Off-Label Use

When new pharmaceuticals are approved for market, the licensing authority specifies the medical condition for which the drug was tested and developed to treat. Physicians may determine, however, that the drug has other potential benefits and prescribe it to treat other disorders. This is called *off-label* use. Examples of off-label use include antipsychotics to treat depression, anticonvulsants to treat pain, and antidepressants to treat sexual dysfunction in men. It sometimes happens that a drug works surprisingly well for its off-label prescription. An example of this is the drug bupropion. It was developed originally as an antidepressant and given the trade name Wellbutrin. Later, it was coincidently discovered that bupropion reduced smoking in people who took it. Clinical trials were conducted, and its effectiveness in helping people quit smoking was confirmed. Now, in addition to being marketed as an antidepressant, bupropion is marketed as Zyban, a smoking-cessation aid.

drug development). During development and marketing of a new drug, the company can patent that drug for a certain time so that no other company can sell it. Drug patents are typically granted for about a 20-year period from the initial application date. By the time the drug is fully developed and granted approval for sale, about 7 to 12 years of patent remain while the drug is on the market. Even though it must use the generic name somewhere in its advertising and documentation, the drug company does not sell the drug under its generic name. Instead, it creates a new name called the *trade name*, *proprietary name*, or *brand name*. Whereas a generic (nonproprietary) name can be used by anyone, a trade (proprietary) name is the property of the company selling the drug and no other company can use that name. The trade name for diazepam is Valium. Once the patent expires, other companies can sell the drug or they can make it under license from the owner of the patent, but they frequently sell it under a different trade name. Therefore, one drug can have many different trade names.

Because drug companies sell their products under trade names, those are the names that people in the medical profession are most familiar with and likely to use. If a physician writes you a prescription, you may not be able to find that drug name listed in this or any other text that uses generic names. Trade names can be distinguished from generic names because their first letter is capitalized.

Strictly speaking, the trade name refers to more than just the active ingredient in the medicine. The active ingredient may be marketed in the form of a pill, powder, aerosol, or liquid that may contain a number of other ingredients—fillers, coloring agents, binding agents, flavors, preservatives, and coatings—collectively referred to as *excipients*. The excipients and the active ingredient are combined in a particular way, and this is known as the drug's *formulation*. Different pharmaceutical companies may market the same drug under different trade names using different formulations. It cannot be assumed that all formulations with the same active ingredient are equal. For example, different formulations may be released immediately or slowly into the body or may dissolve at different rates in different parts of the gastrointestinal tract and, consequently, may not be equally effective.

1.2.4: Street Name

Drugs that are sold on the street for recreational use generally have a street name, which can change with time and differ geographically. Usually, though, a particular drug has one street name that is widely recognized. For example, the club drug MDMA (3,4-methylenedioxymethamphetamine) is commonly referred to by the street name *ecstasy*. Many drugs used recreationally are not manufactured by drug companies and prescribed by physicians to treat disease or illness. However, sometimes pharmaceutical drugs are diverted from medical use and sold on the street. Street names for diazepam (Valium) include tranks, downers, blue Vs, old joes, and drunk pills. Select examples of recreationally used pharmaceutical drugs' chemical, generic, trade, and street names are provided in Table 1-2.

1.3: Describing Dosages

All of modern science uses the metric system and drug doses are nearly always stated in *milligrams* (mg). A milligram is 1/1,000 of a gram (there are a little over 28 grams in an ounce). It is generally true that the behavioral and physiological effects of a drug are related to its concentration in the body rather than the absolute amount of drug administered. If the same amount of a drug is given to individuals of different weights, it will reach different concentrations in the body and brain of each individual. To ensure that the drug is present in the same concentration in all experimental participants or patients, different doses are frequently given according to body weight. For this reason, in research papers, doses are usually reported in terms of milligrams per kilogram (kg) of body weight—for example, 6.5 mg/kg (a kilogram is equal to 2.2 pounds).

Reporting doses in this manner also helps when comparing research on different species. If you account for such factors as metabolic rate and body composition, a dose of 1 mg/kg in a monkey will be roughly equivalent to a dose of 1 mg/kg in a human. Interspecies comparisons, however, can be tricky. Generally, smaller organisms have higher metabolic rates than larger animals. As we shall see later, many drugs are broken down by the body's metabolism. This means that drugs are metabolized faster in smaller animals, so it is often necessary to give them a higher dose if they are to reach an exposure equivalent to that of a human. Thus, a dose of 1.0 mg/kg in a human may be equivalent to a dose of 10.0 mg/kg in a mouse or rat. For this reason, research done with rats and mice often uses doses that appear excessive in human terms.

1.3.1: Dose–Response Curves

To establish a true picture of the physiological and behavioral effects of a drug, it is usually necessary to give a wide range of drug doses. The range should include a dose so low that there is no detectable effect, a dose so high that increases in dose have no further effect, and a number of doses in between. The effect of this range of doses is plotted on a graph, with the dose indicated on the horizontal axis and the effect on the vertical axis. This type of figure is called a *dose–effect curve (DEC)* or a *dose–response curve (DRC)*. It is generally found that a small change in low doses can have a big effect, but an equally small change in a large dose has no effect. Plotting doses so that the scale on the horizontal axis is graduated logarithmically allows a wide range of doses to be reported and permits greater precision at the low end of the dosage range.

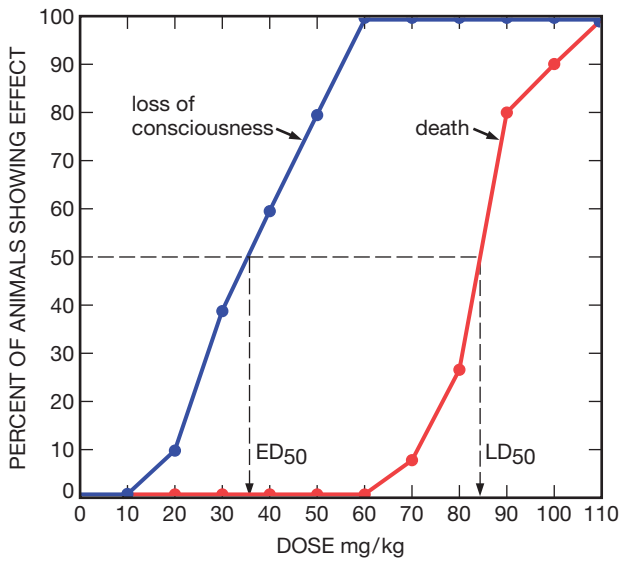
Oftentimes, the vertical axis will represent a continuous measure, such as response rate, latency to respond, or percentage performance compared to a control group. But there are other types of DRCs in which the effect is a discrete binary variable rather than a continuous one. For example, we could not use a continuous scale if we wanted to report a DRC for the effectiveness of a drug as an anesthetic. Either subjects are anesthetized or they are not! If the vertical axis simply read *Yes* or *No*, we would not have any sort of a curve. When a binary variable is used, DRCs are constructed differently.

Binary drug effects are handled by working with groups of subjects. Each group is given a different dose of the drug, and the percentage of subjects in each group that shows the effect is then plotted. An example of this type of DRC is given in Figure 1-1. This hypothetical experiment is designed to establish the DRC for loss of consciousness and the lethal effects (another clearly binary variable) of a fictitious new drug: *endital*. In this experiment, there are 12 groups of rats. Each group is given

Table 1-2 Chemical, Generic, Trade, and Street Name Examples

Anxiolytics and Sedative-Hypnotics (Chapter 7)			
Chemical Name	**Generic Name**	**Trade Names**	**Street Names**
8-chloro-1-methyl-6-phenyl-4H-[1,2,4] triazolo[4,3-a][1,4]benzodiazepine	alprazolam	Xanax	benzos; bicycle parts; blue footballs; handlebars; school bus; totem poles; Upjohn; xanbars; xannies
5-ethyl-5-phenyl-1,3-diazinane-2,4,6-trione	phenobarbital	Luminal; Nembutal	abbots; barbs; goofballs; Mexican yellows; nembies; phennies; purple hearts; red birds; tooies; yellow jackets
Psychomotor Stimulants (Chapter 10)			
Chemical Name	**Generic Name**	**Trade Names**	**Street Names**
methyl[(2S)-1-phenylpropan-2-yl]amine	methamphetamine	Desoxyn	chaulk; crank; crystal; glass; ice; meth; speed; yaba
1-phenylpropan-2-amine	amphetamine	Dexedrine; Adderall	ampes; bennies; black beauties; blue Mollies; Christmas trees; dexies; eye poppers; lightening; pep pills; uppers
methyl 2-phenyl-2-(piperidin-2-yl)acetate	methylphenidate	Ritalin; Concerta; Metadate; Methylin, Focalin	crackers; kibbles and bits; kiddy coke; pineapple; poor man's cocaine; R-ball; skippy; skittles; smarties; study buddies; vitamin R; west coast
Opioids (Chapter 11)			
Chemical Name	**Generic Name**	**Trade Names**	**Street Names**
4,5α-epoxy-3,14-dihydroxy-17-methylmorphinan-6-one	oxymorphone	Opana; Numorphan	blue heaven; Mrs. O; octagons; oranges; pink lady; stop signs; the O bomb
N-(1-(2-phenylethyl)-4-piperidinyl)-N-phenylpropanamide	fentanyl	Sublimaze; Actiq; Fantora; Duragesic	Apache; China white; dance fever; friend; goodfella; jackpot; murder 8; Tango and Cash; TNT
6-(dimethylamino)-4,4-diphenylheptan-3-one	methadone	Dolophine; Methadose	amidone; chocolate chip cookies; dollies; fizzies; jungle juice; junk; metho; wafer
Hallucinogens, Psychedelics, and Club Drugs (Chapter 15)			
Chemical Name	**Generic Name**	**Trade Names**	**Street Names**
4-hydroxybutanoate	gamma-hydroxybutyrate (GHB)	Xyrem	easy lay; G; Georgia home boy; goop; grievous bodily harm; liquid ecstasy; liquid X; scoop
2-(2-chlorophenyl)-2-(methylamino) cyclohexan-1-one	ketamine	Ketalar	cat Valium; jet; K; purple; special LA coke; special K, super acid; vitamin K

Figure 1-1 Results of a hypothetical experiment using 12 groups of rats. Each group was given a different dose of enditol, ranging from 0.0 (a placebo) to 110 mg/kg. One curve shows the percentage of animals in each group that lost consciousness; the other curve shows the percentage that died at each dose. The ED_{50} and the LD_{50} are also indicated.



a different dose of endital—from 0 mg/kg (a placebo) to 110 mg/kg—represented on the graph's horizontal axis. The graph's vertical axis represents the percentage of rats in each group that showed the effect. The curve on the left shows how many rats lost consciousness, and the curve on the right shows the percentage of rats in each group that died. These curves inform us of endital's effectiveness and lethality.

ED_{50} AND LD_{50} A common way of describing dose–response curves and comparing the effectiveness of different drugs is by using the *ED_{50}, the median effective dose*, or the dose that is effective in 50% of the individuals tested. Figure 1-1 indicates that the ED_{50} for losing consciousness from endital is 35 mg/kg. By checking the next curve, you can see that the dose of endital that killed 50% of the rats was 84 mg/kg. This is known as the *median lethal dose*, or the *LD_{50}*.

It is also common to use this shorthand to refer to lethal and effective doses that are not at the median. For example, the LD_{50} is the dose at which 50% of subjects die, the LD_1 is the dose that kills 1% of subjects, and the ED_{99} is the dose that is effective in 99% of all cases. In DRCs constructed from continuous rather than binary measures, the

ED_{50} refers to the dose that produces an effect that is 50% of the drug's maximally effective dose.

1.3.2: Drug Safety

When a new drug is being developed and tested, it is common to establish the LD_{50} and the ED_{50} to give an idea of its safety. The farther the lethal dose is from the effective dose, the safer the drug. The *therapeutic index* (TI; also known as the *therapeutic ratio*) is sometimes used to describe the safety of a drug. This is the ratio of the LD_{50} to the ED_{50}; $TI = LD_{50}/ED_{50}$. The higher the TI, the safer the drug. The TI of endital calculated from Figure 1-1 would be 84/35 = 2.4. Drug safety may also be described as a ratio of the ED_{99} and the LD_1.

1.4: Potency and Effectiveness

Potency and *effectiveness* (or *efficacy*) are terms that are sometimes used to describe the extent of a drug's effect. The two terms do not mean the same thing. When you are comparing two drugs that have the same effect, *potency* refers to differences in the ED_{50} of the drugs. The drug with the lower ED_{50} is more potent. For example, if you constructed two DRCs for *lysergic acid diethylamide* (LSD) and *lysergic acid amide* (LSA; a related compound found in morning glory seeds) for the ability to cause hallucinations, you would find that the ED_{50} of LSA is 10 times higher than that of LSD. In other words, the nature and extent of the effect of LSA would be the same as that of LSD if you increased the dose of LSA by a factor of 10—LSD is 10 times more potent than LSA.

Effectiveness refers to a drug's ability to produce a maximum, biologically functional response at its molecular target, regardless of dose. Both acetylsalicylic acid (Aspirin) and morphine are analgesics or painkillers. When dealing with severe pain, Aspirin at its most effective dose is not as effective as morphine. To compare these two drugs in terms of potency would not be appropriate. They might both produce analgesia at the same dose and, thus, be equally potent, but the extent of the analgesia would be vastly different. The difference between potency and effectiveness is shown in Figure 1-2.

1.5: Drug Interactions

When two drugs are mixed together their effects can interact in several ways. If one drug diminishes the effect of another, this interaction is called *antagonism*. Drug antagonism is established by plotting two DRCs: one for the drug alone, and a second for the drug in the presence of the other drug. If the DRC for the first drug is shifted to the right (i.e., the ED_{50} increases) by adding the new drug, this result indicates antagonism between the drugs.

If adding the new drug shifts the DRC to the left (i.e., the ED_{50} decreases), the drugs are said to have an *additive effect*. If, together, drugs have an effect that is greater than might be expected simply by combining their individual effects, a *superadditive effect*, or *potentiation*, exists. This can be particularly dangerous if the drugs' effects include respiratory depression, as is the case with alcohol and tranquilizing drugs (barbiturates). It is not always obvious whether a drug interaction is additive or superadditive, but in one situation the distinction is clear: if one drug has no effect alone but increases the effect of a second drug, potentiation is clearly occurring.

In these examples, drug interaction is defined in terms of changes in potency—shifts in the DRC indicated by changes in the ED_{50}. Interactions between drugs can also change their effectiveness. That is, the ED_{50} may not change, but the maximum effect may increase or decrease (see Figure 1-3).

Figure 1-2 Left: Drugs A and B are equally effective, but the potency of Drug A is greater than that of Drug B. Right: Drugs C and D are equally potent, but the effectiveness of Drug C is greater than that of Drug D.

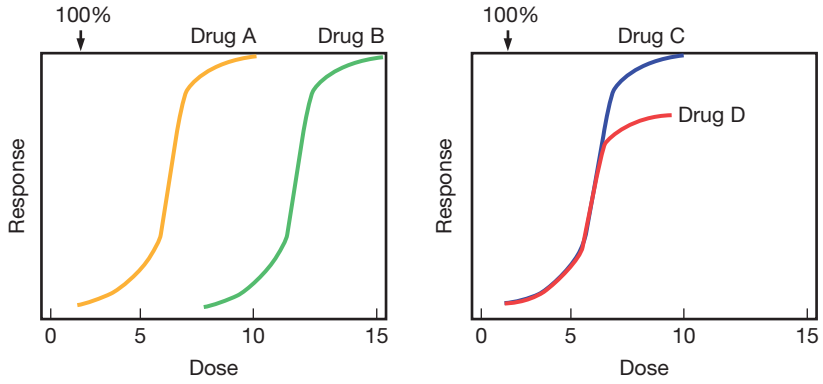
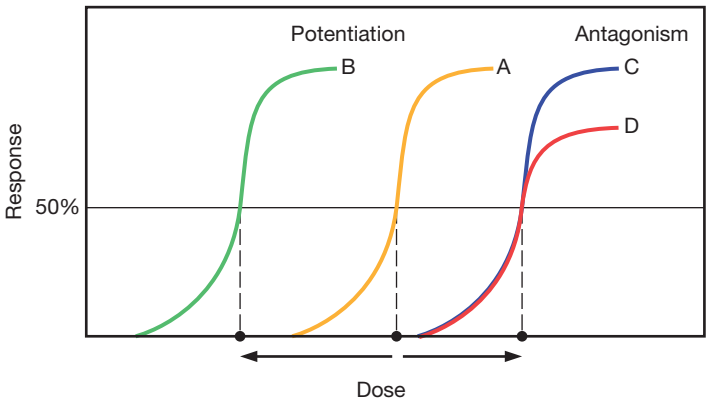


Figure 1-3 Drug interactions. The curve labeled A is the dose–response curve (DRC) for a drug, against which the effects of the addition of other drugs will be compared. The curve labeled B shows the DRC after the administration of a second drug. Note that the DRC has been shifted to the left and the ED_{50} has decreased. This indicates potentiation or an additive effect. Curve C is the DRC after another drug has been given. This drug has shifted the DRC to the right, increasing the ED_{50}. This indicates antagonism. Curve D shows the effect of another drug on the DRC. In this case the DRC has been shifted to the right, showing a decrease of potency, and the maximum effect has also been reduced showing a decrease in effectiveness.



1.6: Primary Effects and Side Effects

It is generally accepted that no drug has only one effect, though in most cases only one effect is wanted. It is common to call the effect for which a drug is taken the *primary* or *main effect* and any other effect, harmful or otherwise, is a *side effect*. Often, the distinction between main and side effects is a matter of intention. Aspirin, for example, has several physiological effects: it brings down fever, it reduces swelling and inflammation, and it slows the blood's ability to clot. If you take Aspirin to reduce a fever, the temperature-lowering effect is the primary effect, and the other two are side effects. The inhibition of blood clotting is a potentially harmful effect because it can cause bleeding into the stomach, which can have serious consequences. But this anticlotting effect can be useful. Strokes are caused by a clot of blood getting caught in the brain. Taking low-dose Aspirin every day can reduce the chance of stroke in people at risk. In this case, the anticlotting effect would be the primary effect, and any other effects that the Aspirin might be having would be the side effects. When new behaviorally active drugs are developed to treat diseases, the ability of a drug to be abused or to create an addiction is considered a dangerous side effect. To a drug user, however, this psychological effect of the drug is vitally important, and any other effects the drug may have on the body are considered unimportant or undesirable side effects.

1.7: Pharmacokinetics

The study of how a drug moves around the body is called *pharmacokinetics*. Pharmacokinetics includes three processes: *absorption*—how a drug gets into the blood; *distribution*—where it goes in the body; and *elimination*—how the drug is broken down and leaves the body. Drugs do not have an effect on all body tissues. As a matter of fact, most drugs influence the operation of the body only at specific and limited places, called *sites of action*. A drug may get into the body, but it will have no effect unless it gets to its site of action where it will interact with a cell to change the cell's biochemical processes. It is, therefore, important to understand how drugs get from their place of administration to the place where they act.

1.8: Routes of Administration

Some foods and medications may contain large amounts of valuable nourishment and medicine, but simply swallowing them or otherwise putting them into the body is no guarantee that they will get to their site of action to exert their desired effect. It is also true that the way a substance is administered can determine its *bioavailability*—that is, not only whether it gets to its site of action, but also how fast it gets there and how much of it gets there.

A route of administration refers to the method used to get a drug from outside the body to some place under

the skin. Some substances can be directly absorbed through the skin, but most cannot. Getting drugs into the body can be accomplished by taking advantage of the body's natural mechanisms for taking substances inside itself (such as digestion, breathing, or absorption through mucous membranes), or the drug can be artificially placed under the skin by means of injection.

1.8.1: Parenteral Routes of Administration

Parenteral routes of administration involve injection through the skin into various parts of the body, using a hollow needle and syringe. Parenteral routes are further subdivided, depending on where in the body the drug is injected.

VEHICLE Before a drug can be injected, it must be in a form that can pass through a syringe and needle—that is, it must be liquid. Because most drugs are in a dry powder or crystalline form (the word *drug* is derived from the French *drogue*, meaning *dry powder*), it is necessary to dissolve or suspend a drug in some liquid before it can be injected. This liquid is called a *vehicle*. Most behaviorally active drugs tend to dissolve well in water and remain stable for long periods of time in water solution. Pure water is not totally inert with respect to the physiology of the body, so a weak salt solution is used instead. Because body fluids contain dissolved salts, the most common vehicle is *normal* or *physiological saline*, a solution of 0.9% sodium chloride (ordinary table salt), which matches body fluids in concentration and does not irritate the tissues when it is injected, as pure water would.

In some cases, the drug to be injected does not dissolve in water. The primary psychoactive ingredient in marijuana, tetrahydrocannabinol (THC), is an example of such a drug; it requires a different vehicle, such as vegetable oil (see Chapter 14). Administering lipid-soluble drugs in an oil vehicle slows the rate of absorption, prolonging the drug's effects over several days.

When a drug is in liquid form and the syringe is filled, the needle can be inserted into various places in the body, and the drug and vehicle are then injected to form a small bubble, or *bolus*. There are four common parenteral routes, depending on the site where the bolus containing the drug is to be placed: (a) *subcutaneous*, (b) *intramuscular*, (c) *intraperitoneal*, and (d) *intravenous*.

SUBCUTANEOUS In published material, the term *subcutaneous* is frequently abbreviated *s.c.* In jargon, it is called *sub-q*. As the name suggests, in this route of administration, the drug is injected to form a bolus just under the skin or cutaneous tissue. In most laboratory animals, the injection is usually made into the loose skin on the back, between the shoulders. For medical purposes in humans, s.c. injections are usually done under the skin of the arm or thigh, but the hand or wrist is sometimes used to self-administer recreational drugs such as heroin, a procedure referred to as *skin popping*. Some drugs, including contraceptives, may be manufactured as pellets for s.c. implantation, which prolongs absorption, sometimes for years.

INTRAMUSCULAR In the *intramuscular* (*i.m.*) route, the needle is inserted into a muscle, and a bolus is left there. Depot injections (discussed below) are administered intramuscularly. In humans, the most common muscle used for this purpose is the *deltoid* muscle of the upper arm or the *gluteus maximus* muscle of the buttock. To receive such an injection, the muscle must be fairly large, so i.m. injections are seldom given to rats and mice. They are more frequently given to monkeys. This route of administration is common for pigeons as well; the injection is given into the large breast muscle. Drugs administered i.m. are typically absorbed through the muscle's capillaries within roughly an hour.

INTRAPERITONEAL The abbreviation for the *intraperitoneal* route is *i.p.*, and, as the name suggests, the needle is inserted directly into the peritoneal cavity. The *peritoneum* is the sack containing the visceral organs, such as the intestines, liver, and spleen. The aim of an i.p. injection is to insert the needle through the stomach muscle and inject the drug into the cavity that surrounds the viscera. It is not desirable to inject the drug directly into the stomach or any of the other organs. Doing so could be harmful and cause hemorrhaging and death. At the very least, injection into an organ is likely to alter the reaction to the drug.

Intraperitoneal injections are commonly used with rats and mice because they are easy and safe and cause the animals very little discomfort. They are much less convenient in larger animals and are almost never given to humans. At one time, rabies vaccine was commonly given to humans via this route, but this is no longer the case.

INTRAVENOUS In an *intravenous* (*i.v.*) injection, the needle is inserted into a vein and the drug is injected directly into the bloodstream. Colloquially, this is referred to as *mainlining*. Before an i.v. injection can be given, it is necessary to find a vein that comes close enough to the surface of the skin that it can be pierced with a needle. In humans, this is usually the vein on the inside of the elbow. The most common procedure is to wrap a tourniquet around the upper arm between the injection site and the heart. Because veins carry blood toward the heart, the tourniquet will dilate or enlarge the vein at the injection site and make injection easier.

When the end of the needle is inserted into the vein, the tourniquet is removed, and the drug is injected when

normal blood flow has resumed. This is essentially the reverse of the procedure used when blood is removed for a blood test. When a drug is administered i.v., it gets distributed throughout the body very quickly, reaching the brain in a matter of seconds and producing rapid effects. One difficulty with i.v. injections, however, is that a vein cannot be used too frequently or it will collapse and simply stop carrying blood. When veins have collapsed in the arms, other veins in the wrists, hands, and feet may be used, but they are more difficult to strike accurately with a needle. Another problem is that recreational drugs may contain contaminants that are insoluble (do not dissolve) and, once in the bloodstream, become lodged in and cause damage to small blood vessels in organs such as the lungs or eyes.

In laboratory animals, i.v. injections are not commonly used by behavioral pharmacologists because veins close to the surface of the skin are unusual in rats, mice, and pigeons, and the procedure is not easy in unrestrained animals. Fur and feathers also make veins difficult to locate. When i.v. injections are necessary, they are usually accomplished by means of a permanently implanted tube called a *catheter*. In rodents and monkeys, *venous* (in a vein) catheters are usually inserted in the jugular vein in the neck, and the free end of the tube emerges from the animal's back. When an intravenous injection is required, the syringe is attached to the end of the catheter outside the body, and the drug is injected. Researchers frequently use this type of preparation to study self-administration of drugs by animals (the catheter may be attached to a motor-driven pump that the animal can control by pressing a lever). Intravenous catheters are fairly permanent and may last for months before they have to be replaced.

OTHER PARENTERAL ROUTES Experimental research with laboratory animals sometimes involves injections directly into the central nervous system (the brain and spinal cord; see Chapter 4). In *intrathecal* injections, for example, the needle is inserted into the nervous system between the base of the skull and the first vertebra. The drug is left in the *cerebrospinal fluid* (CSF; the fluid that bathes the nervous system) and quickly diffuses throughout the nervous system. A drug may also reach the CSF through an *intracerebroventricular* injection directly into one of the brain's *ventricles*, which are chambers filled with CSF. To more precisely determine drug effects on specific areas of the brain, *intracerebral* injections may be used in which a drug is administered directly into brain tissue. These forms of drug administration are often done through a *cannula*. A cannula is like a catheter, except it is a rigid tube resembling a hypodermic needle. Cannulae are often attached to the skull using dental cement and can remain permanently implanted.

ABSORPTION FROM PARENTERAL SITES With intravenous injections, the drug is put directly into the bloodstream. But when injected at other sites, the drug must be absorbed into the circulatory system. The rate at which a drug gets from an injection site into the blood is determined by a number of factors associated with blood flow to the area. Generally, the volume of blood flow is greater to the peritoneal cavity than to the muscles, and it is greater to the muscles than under the skin. As a result, next to an i.v. injection, absorption is fastest from an i.p. injection and is slowest from an s.c. injection.

Heat and exercise can speed absorption from i.m. and s.c. sites because such factors increase blood flow to muscles and skin. Thus, an i.m. injection will be absorbed faster if the muscle is exercised after the injection, and the drug from a subcutaneous site will get into the blood faster if heat is applied to the area and more slowly if the area is chilled.

To be absorbed into the bloodstream, a drug must pass through the walls of the capillaries. A *capillary* is a tiny vessel through which blood flows. Capillaries permeate most body tissues. They are so small in diameter that red blood cells can barely pass through. It is through the walls of capillaries that nutrients and oxygen pass out of the blood into body tissues, and it is also through these capillary walls that waste products and carbon dioxide pass into the blood and are removed. Blood leaves the heart and is distributed around the body in *arteries*. The arteries divide into smaller and smaller branches until they become capillaries. The blood in capillaries is eventually collected in *veins*, which carry the blood back to the heart and the lungs (see Figure 1-4).

The walls of the capillaries are made up of a single layer of cells. Between these cells are small openings, or *pores*, through which nutrients, waste products, and drugs may pass freely. The only substances in the blood that cannot move in and out of the capillaries through these pores are red blood cells and large protein molecules, which are trapped inside because they are larger than the pores.

Injected drugs pass into capillaries and the bloodstream through these pores by simple *diffusion*. Diffusion is the process by which a substance tends to move from an area of high concentration to an area of low concentration until the concentrations are equal in both areas. If a drop of food coloring is placed in the corner of a tub of still water, it will remain as a highly colored drop for only a short period of time. The force of diffusion will soon distribute the coloring evenly throughout the tub of water. The same principle determines that a drug injected into a muscle or under the skin will move from the area of high concentration (the bolus at the site of the injection) into the blood, an area of low concentration, until the concentrations in the two places are equal. The drug from an injection site will move through the pores into the blood in the capillaries surrounding the injection site. Because this blood is constantly circulating and being replaced by new blood with a