DRUGS AND BEHAVIOR

An Introduction to Behavioral Pharmacology

FOURTH EDITION

WILLIAM A. MCKIM

Drugs and Behavior

An Introduction to Behavioral Pharmacology

Fourth Edition

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Library of Congress Cataloging-in-Publication Data

McKim, William A.
Drugs and behavior : an introduction to behavioral pharmacology / William A. McKim.—4th ed.
p. cm.
Includes bibliographical references and index.
ISBN 0-13-083146-8
1. Psychopharmacology. 2. Psychotropic drugs. I. Title.
RM315.M36 2000
615′.78—dc21 99-046144

Editor-in-Chief: *Nancy Roberts*
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This book was set in 10/12 Times Roman by Publications Development Company of Texas and was printed and bound by RR Donnelley & Sons Company. The cover was printed by Phoenix Color Corporation.

Printed in the United States of America
10 9 8 7 6 5 4 3 2 1

ISBN 0-13-083146-8

Prentice-Hall International (UK) Limited, *London*
Prentice-Hall of Australia Pty. Limited, *Sydney*
Prentice-Hall Canada Inc., *Toronto*
Prentice-Hall Hispanoamericana, S.A., *Mexico*
Prentice-Hall of India Private Limited, *New Delhi*
Prentice-Hall of Japan, Inc., *Tokyo*
Pearson Education Asia Pte. Ltd., *Singapore*
Editora Prentice-Hall do Brasil, Ltda., *Rio de Janeiro*

To
B.F. Skinner
who made Behavioral Pharmacology possible
and to the pioneers who made it happen. These include, but are not limited to,
Jim Barrett, Herb Barry, Joe Brady, Len Cook, Peter Dews, John Falk,
Murray Jarvick, Roger Kelleher, Conan Kornetsky, Vic Laties, Bill Morse,
Don Overton, Bob Schuster, Lew Seiden, Travis Thompson, and Jim Weeks.

Preface

The study of drug use and drug effects is fast moving and exciting; it is a rapidly expanding field where new developments, discoveries, and insights are happening every day. Perhaps one of the more exciting aspects of drug research is that it is truly multidisciplinary, encompassing pharmacology, neuroanatomy, neurophysiology, epidemiology, endocrinology, and psychology, to name a few. This text is primarily about the application of behavioral research (traditionally referred to as psychology) to understanding the effects of drugs and the use of drugs. Because the field is made up of so many disciplines, it is impossible to consider the role of behavioral science in isolation. In this book, the role of behavioral research is placed in the context of the contributions of these other disciplines.

Within the last few years, most of the serious advances in drug research have been made in the area of psychology and neuroscience, inspiring a new edition of Drugs and Behavior. In addition, most of the effort of researchers has been in understanding drug use and addiction rather than the effects of drugs. This emphasis is reflected in the Fourth Edition which has an expanded chapter on Addiction and Dependence (Chapter 5) and an expanded and updated chapter in neuroscience (Chapter 4). An attempt has been made in these two chapters to explain the most recent ideas on how drugs affect the circuits in the brain that control behavior, and in particular, the motivational circuits responsible for the use of drugs. Where information is available, the discussion of the self-administration of specific drugs in each chapter incorporates this information as well.

To help in this focus, I have taken on a co-author for Chapter 4. He is R.A.M. Brown. Bob provided his expertise in making sure that the neuroscience reported in Chapter 4 and throughout the book is as current as possible, and explained in a easily comprehensible manner. Among the many other improvements, Chapter 4 now contains information on how neurotransmitters and neuromodulators are capable of altering the functioning of nerve cells over a range of times that extend from brief membrane potential changes that alter cell excitability for milliseconds to permanent changes in the transcription of DNA.

Unlike the first three editions, the fourth edition does not have a glossary. I have attempted to design the index to fill the function of a glossary. You will notice that for the entries for important concepts, the page of the definitive discussion of the concept is indicated in bold print. This should permit the student to instantly locate the appropriate definition of any concept as well as a more extended discussion of it, not just a cursory and necessarily constrained glossary definition.

This book would not have been possible without the assistance of many people. These include those mentioned in the earlier editions. In this edition, I would like to acknowledge the help of my wife who not only assisted with many technical matters but tolerated my absence while the book was being written, my colleagues, both at Memorial University and many other institutions around the world who read many drafts, sent me manuscripts, pointed out many errors and made many suggestions, my students who suffered through many teaching experiments and nearly unreadable drafts of the manuscript, and the technical and office staff in the Psychology Department at Memorial University. All these people include, but are not limited to Geoff Carre, Marilyn Carroll, Harriet de Wit, Shola Elabanjo, Kim French, Carolyn Harley, John Harvey, Bow Tong Lett, Gerard Martin, Andrew McKim, Edna McKim, Heather McKim, Kathleen McKim, Brenda Noftle, John Podd, Sam Revusky, Brandi Smith, John Scott, Bernice St. Croix, Bernie Weiss, Bill Wolverton, and Jim Zacny.

I would also like to acknowledge the helpful comments of John P. Broida at the University of Southern Maine who reviewed this manuscript for the publisher.

Apart from taking credit where such is due, none of these people can be held in any way responsible for any errors or problems in the book because I did not always follow the advice I was given.

WILLIAM A. MCKIM

St. John's
August 1999

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CHAPTER 1

Some Basic Pharmacology

WHAT IS A DRUG?

Most people understand what is meant by the term *drug,* but, surprisingly, coming up with a precise definition is not all that easy. The traditional way is to define a drug as any substance that alters the physiology of the body. This definition, however, includes food and nutrients, which are not usually thought of 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.* This definition usually works, but it still leaves a lot to be desired. To begin with, the distinction between a drug and a nutrient is not at all clear. Vitamin C, for example, alters physiology, but is it a drug? If it is consumed in the form of an orange, it is clearly food, but if taken as a tablet to remedy a cold, it could be thought of as a drug.

Similarly, some substances that alter the physiology of the body may best be thought of as *toxins* or poisons rather than drugs, and may not be deliberately consumed. Gasoline and solvent vapors are examples. If they are consumed deliberately, to get high, they might be drugs, but when inhaled unintentionally in the workplace they may be called environmental toxins. The exact distinction between a toxin and a drug is not clear.

One element that complicates the definition appears to be the intention of the drug user. If a substance is consumed to get high or to treat a disorder, it is clearly best to think of it as a drug, but if it is consumed for taste or sustenance, it may not be useful to think of it as a drug. Such a debate has been waged about caffeine. As you will see in Chapter 9, caffeine clearly alters human physiology, but it also has been 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 context. If the soft drink is consumed because of the effect caffeine has on the nervous system, then it is appropriate to think of it as a drug. A similar debate has been waged about the role of nicotine in tobacco (see Chapter 8). In these cases, the consequences are important

to government regulatory agencies and various manufacturers. Fortunately, it is not necessary for us to form a precise definition of a drug. An intuitive definition will serve our purposes. However, we should never lose sight of the fact that any one definition may not be appropriate in all circumstances.

NAMES OF DRUGS

One of the more confusing things about studying drugs is their names. Most 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.

Chemical Name

All drugs have a *chemical name,* stated in formal chemical jargon. A chemist can usually tell by looking at the name what the molecule of the drug looks like. Here is the chemical name of a drug:

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

As you can see, it is full of chemical terminology, letters, and numbers. The numbers 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.

Generic Name

When a drug becomes established, its chemical name is too clumsy to be useful, so a new, shorter name is made up for it—a *generic name* or *nonproprietary name.* The generic name for the drug whose chemical name we just struggled through is *diazepam.* A drug's generic name bears some resemblance to its chemical name. The conventions for making up generic names are handy to know because they are clues to the nature of the drug. For example, most barbiturate drugs end in *-al,* like secobarbital, and most local anesthetics end in *-caine,* as in procaine.

For the most part, textbooks (including this book) and scientific discussions of drugs use generic names.

Another type of name is being used more and more. When new substances are created by drug companies, they may be used extensively before generic names can be established. Instead of their chemical names, these drugs are sometimes referred to by a code using letters and numbers—for example, *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.

Trade Name

When a drug company invents and develops a new drug, often at a cost of millions of dollars, it can patent the drug for a number of years so that no other company can sell it. The drug company does not sell the drug under its generic name. Instead, it makes up a new name called the *trade name* or *proprietary name.* The trade name is the property of the company that sells the drug, and no other company can use it (hence, the name is proprietary). The trade name for the drug we have been discussing is Valium. After 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, people in the medical profession are most familiar with trade names and are most likely to use them. If a physician

gives you a prescription for a drug and you are told the name of the drug, you may not be able to find it listed in this or any other text that uses generic names. Trade names can be distinguished from generic names because the first letter is capitalized.

Strictly speaking, the trade name refers to more than the active ingredient in the medicine; it refers to the *formulation.* The active ingredient is marketed in the form of a pill, tablet, or capsule that may contain a number of other ingredients—fillers, coloring agents, binding agents, 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 formulation. Different pharmaceutical companies may market the same drug, but in different formulations that are given different trade names. It cannot be assumed that all formulations with the same active ingredient are equal. For example, different formulations may dissolve at different rates in different parts of the digestive system and consequently may not be equally effective.

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 effect of a drug is 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 sizes, the drug will reach a different concentration in the body of each individual. To ensure that the drug is present in the same concentration in the brains of all subjects or patients, different doses are 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 other factors as metabolic rate and body composition, a dose of 1 mg/kg in a monkey will be roughly comparable to a dose of 1 mg/kg in a human.

Dose Response Curves

To get a true picture of the effect of a drug, it is usually necessary to give a range of doses of the drug. The range should cover a dose so low that there is no detectable effect and a dose so high that increases in dose have no further effect. It is usual to plot the effect of this range of doses 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 response curve* (DRC). Figure 1–1 shows a typical DRC. It indicates the effect of caffeine on a mouse's rate of responding on an FI schedule. (Schedules will be explained in Chapter 2.)

Note that the scale on the horizontal axis is graduated logarithmically. 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 on a log scale allows a wide range of doses to be reported and permits greater precision at the low end of the dosage range. Log scales became common when it was found that many physiological effects of a drug showed up as a straight line when plotted on a log scale.

In the example just used, the drug effect was a measure of response rate, 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 this type of curve if we wanted to report a DRC for the effectiveness of a drug as an anesthetic. Subjects are either anesthetized or they are not. If the vertical axis simply read "Yes" or "No," we would

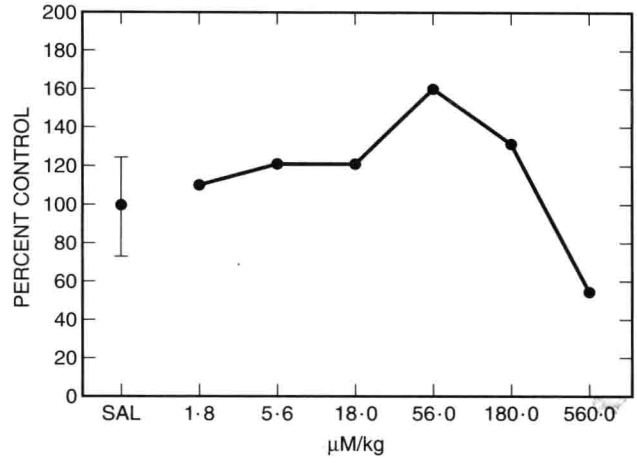

Figure 1–1 The dose response curve for the effect of caffeine on the rate of responding by a mouse being reinforced on an FI schedule with food. (Adapted from McKim, 1980.)

not have any sort of a curve. When a binary variable is used, DRCs are constructed differently and are sometimes referred to as *dose effect curves*.

Problems like these 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 1–2. This hypothetical experiment is designed to establish the DRC for loss of consciousness and the lethal effects of a fictitious new drug, "endital." In this experiment, there are 12 groups of rats. Each group is given a different dose of the fictitious drug, endital, from 0 mg/kg, a placebo, to 110 mg/kg. The vertical axis of the graph shows 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.

ED_{50} and LD_{50}. A common way of describing these 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 percent of the individuals tested. The ED_{50} for losing consciousness from endital in Figure 1–2 is 35 mg/kg. By checking the next curve, you can see that the dose of endital that killed 50 percent 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 percent of subjects die, the LD_1 is the dose that kills 1 percent of subjects, and the ED_{99} is the dose that is effective in 99 percent of cases.

In DRCs where the vertical axis is continuous, the ED_{50} is also used, but, in this case, it refers to a dose that produces an effect that is 50 percent of the maximum effect that the drug causes at any dose.

Drug Safety

When new drugs are being developed and tested, it is common to establish the LD_{50} and the ED_{50} to give an idea of the safety of a drug.